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THE SCHNEIDER INDEX AS MODIFIED BY DISEASES OF THE CIRCULATION

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TESTS of physical fitness have engaged the interest of athletic directors and of medical examiners of the armed forces for many years, and the perfect test has long been sought. What is implied by the term "physical fitness"? As Schneider aptly puts it, "It is used to mean good health." The tests thus far employed number about seventy-two, and may be divided into two groups: performance and nonperformance tests. The performance tests subject the examinee to standard exercise and frequently depend on special skill and cooperativeness. The nonperformance tests, on the other hand, are less influenced by these factors, but the results may be affected by emotion. Endurance tests and tests of muscular strength have been largely discarded because of the need of special skill and adaptability, and these factors are not measures of the general health. Nonperformance tests, which are not accurately named, require less skill and cooperation. The circulatory system, which is so necessary for physical performance, may be studied in its relationship to physical fitness. Many tests have been devised, and the reader is referred to the excellent monograph by Schneider[1] for a detailed description. The Schneider test, alone, is described in detail in these pages because of its wide use today by the army and navy.

Schneider[2] described a method of testing physical fitness in 1920, employing six sets of observations: (1) pulse rate in the reclining position; (2) standing pulse rate; (3) the increase in the pulse rate when standing and recumbent rates are compared; (4) the increase in the pulse rate after standard exercise (stepping on a chair 18 inches high five times); (5) the time required for the heart rate to return to the standing rate after exercise; and (6) the change in the systolic blood pressure when the examinee stands. The scoring of the test is given

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below. A slow pulse initially, a slight increase in the pulse rate on standing and after exercise, a quick fall in pulse rate after exercising, and a rise in systolic blood pressure on standing raise the index.

TABLE I

POINTS OF GRADING CARDIOVASCULAR CHANGES (SCOTT[3])

A. RECLINING PULSE RATE	(POINTS)
50- 60	3
61- 70	3
71- 80	2
81- 90	1
91-100	0
101-110	-1

B. PULSE RATE INCREASE ON STANDING (POINTS)				
0-10	11-18	19-26	27-34	35-42
3	3	2	1	0
3	2	1	0	-1
3	2	0	-1	-2
2	1	-1	-2	-3
1	0	-2	-3	-3
0	-1	-3	-3	-3

C. STANDING PULSE RATE	(POINTS)
60- 70	3
71- 80	3
81- 90	2
91-100	1
101-110	1
111-120	0
121-130	0
131-140	-1

D. PULSE RATE INCREASE IMMEDIATELY AFTER EXERCISE (POINTS)				
0-10	11-20	21-30	31-40	41-50
3	3	2	1	0
3	2	1	0	0
3	2	1	0	-1
2	1	0	-1	-2
1	0	-1	-2	-3
1	-1	-2	-3	-3
0	-2	-3	-3	-3
0	-3	-3	-3	-3

E. RETURN OF PULSE RATE TO STANDING NORMAL AFTER EXERCISE	(POINTS)
0- 30 seconds	3
31- 60 seconds	2
61- 90 seconds	1
91-120 seconds	0
After 120 seconds; 2-10 beats above	-1
11-30 beats above normal	-2

F. SYSTOLIC PRESSURE STANDING COMPARED WITH RECLINING	
Rise of 8 mm. or more	3
Rise of 2-7 mm.	2
No rise	1
Fall of 2-5 mm.	0
Fall of 6 mm. or more	-1

The Schneider method of testing was revised in 1923,[4] and has had wide use in the examination of men applying for admission to the aviation services.

The diurnal variations in the total score were ascertained by Schneider[4] on seven men and seven women. The test was made hourly, and the subjects were kept busy between tests with desk work. They ate the usual meals. The mean score for the men for the twenty-four hours ranged from 10.1 to 13.6, and for the women, from 9 to 14. The largest variations followed eating. The score rose rapidly from 9 A.M. to noon, declined after lunch to 2 P.M., and then rose again until 5 P.M. The evening meal caused another fall. From 8 P.M. to 2 A.M. the index rose, reaching the maximum at 2 A.M. After this there was a slight fall. The effect of conscientious physical training is a higher score. In a study of a football squad by Schneider,[4] the index was lower after discon-

tinuance of training because of acceleration of the heart. Grant[5] states that this test gives an estimate of the efficiency of the cardiovascular system. The average index of commercial air pilots is 14.[6]

The use of this test is dual, i.e., it can be employed both as a screening test and as a method of periodic checkup. Schneider,[1] Armstrong,[7] and Scott[3] caution the student of the subject against drawing conclusions from the test alone, without evaluating all other methods of examination. Likewise, army and navy regulations state that a low index alone is insufficient for disqualification. The scoring is lowered by previous exercise, emotion, infection, excesses of any sort, and by physical deficiencies. Ingestion of food, fatigue, and careless testing affect the score.

Schneider has tested large numbers of normal men, and Scott[3] suggested the following interpretation of scores: excellent, 14-18; very good, 11-13; fair, 9-10; doubtful, 7-8; and unsatisfactory, below 7.

The test must be carefully done. The subject and the examiner must be alone in a quiet room. The preliminary rest must be provided on a comfortable couch or bed. Due consideration to the ingestion of food or liquor, smoking, recent illness, emotion, and fatigue must be given. And, finally, the examiner must appreciate that any test, when taken for the first time, may be poorly performed even by men and women in excellent physical condition, so important are the emotional influences of fear and anxiety.

In the present conflict, with the great demand for large numbers of air recruits, it is most important that unfit men be rejected, and equally important that favorable prospects be accepted. Inasmuch as the Schneider test is widely employed in the examination of aviation recruits, it is important to re-emphasize the limitations of the test.

A careful search of the literature has not revealed any application of the test to patients with known cardiovascular defects. The present observations were undertaken to supply these data.

TABLE II

NORMAL CONTROLS

INSTITUTION	NO.	AGE RANGE	SCORE RANGE	AVERAGE	STANDARD DEVIATION
University School	11	16 to 19	0 to 15	6.91	4.032
Western Reserve	97	18 to 32	2 to 17	10.88	3.328
Lakeside staff	17	23 to 53	6 to 16	12.94	2.775
Miscellaneous	6	15 to 38	0 to 17	10.0	6.0
Women	7	22 to 30	-2 to 18	8.71	6.315
Total	138	15 to 53	-2 to 18	10.68	3.966

Normal Controls.—In order to familiarize ourselves with the index, several groups of normal persons were tested: 138 young, normal adults in all. The scores are tabulated in Table II.

The tests on the seventeen members of the staff of Lakeside Hospital were especially valuable because there was no emotional factor. In this group the average resting pulse rate was 74; the average increase

of the standing pulse rate was 11; the average increase after exercise was 15, and the average time of the return of the pulse rate to the previous standing level was thirty seconds. The average change in blood pressure after standing two minutes was an increase of 7 mm. Hg. The average index of the group was 12.94.

TABLE III

EFFECT OF DIGITALIS ON NORMALS

	CONTROL SCORE	DIGITALIZED SCORE	AMOUNT DIGITALIS
1.	16	10	1.6 Gm.
2.	6	-3	1.4 Gm.
3.	14	13	1.2 Gm.
4.	16	16	1.3 Gm.
5.	16	15	1.2 Gm.
6.	16	9	1.3 Gm.
7.	10	8	1.5 Gm.
8.	14	9	1.2 Gm.
9.	15	7	1.2 Gm.
10.	14	16	1.6 Gm.

The Effect of Digitalis on the Index of Normal Controls.—The medical house officers were the subjects of this study. The test was done before and after digitalization (Table III). Digitalis was given in the following manner: Two doses of 0.5 Gm. of U.S.P. powder were given six hours apart, and 0.2 Gm. was given at intervals of six hours until nausea occurred. The index in the control observations was, with one exception, within the "fair" to "excellent" range. After digitalization the index was lower in eight instances, slightly higher in one case, and unchanged in one case. The reduction in the index was due to the slower return of the heart rate, after exercise, to the previous standing level. This (delay in the return of the pulse rate to the previous standing level after exercise) is in agreement with the observations of Parkinson[8] in cases of soldiers' heart.

TABLE IV

HEART CONDITIONS

SUMMARY

CONDITION	NO.	AGE RANGE	SCORE RANGE	AVERAGE	STANDARD DEVIATION
Aortic insufficiency	2	37, 47	11, 16	13.5	2.5
Auricular fibrillation, idiopathic	2	35, 43	3, 13	8.0	5.0
Arteriosclerotic heart disease	13	41 to 78	4 to 15	9.92	3.647
Coronary thrombosis	16	33 to 59	6 to 16	10.63	3.016
Hypertensive heart disease	37	39 to 66	-1 to 16	9.81	4.05
Rheumatic heart disease	51	13 to 68	-3 to 17	10.1	4.736
Miscellaneous	5	19 to 72	4 to 13	9.2	3.2
Total	126	13 to 78	-3 to 17	10.05	4.24

The Schneider Test in Various Pathologic Conditions.—The test was performed on 121 patients with various diseases of the circulatory system, and on five patients with miscellaneous conditions. All of the

TABLE V

SCORES

CONTROLS CONTRASTED WITH HEART CASES

	CONTROLS		HEART CASES	
	NUMBER	PER CENT	NUMBER	PER CENT
Excellent (14-18)	34	24.6	29	23.0
Very good (11-13)	47	34.1	38	30.2
Fair (9-10)	22	15.9	18	14.3
Doubtful (7-8)	11	8.0	13	10.3
Unsatisfactory (below 7)	24	17.4	28	22.2
Total	138		126	

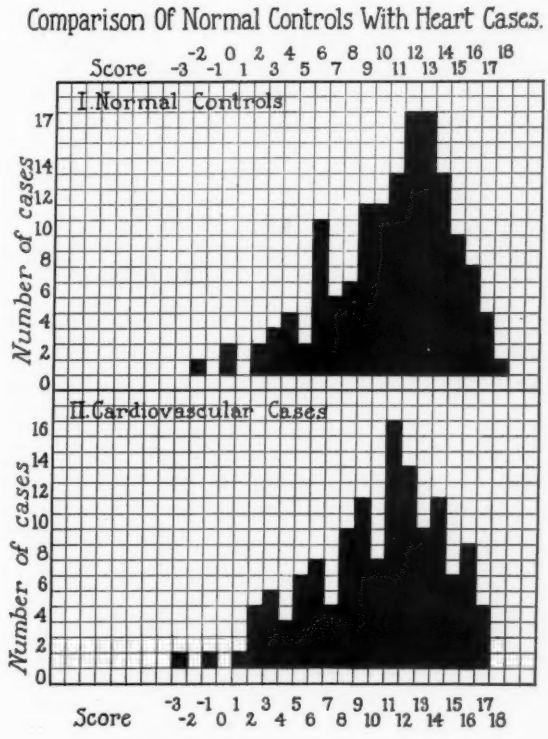
Comparison Of Normal Controls With Heart Cases.
Score -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
I. Normal Controls
Number of cases
II. Cardiovascular Cases
Number of cases
Score -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Fig. 1.

patients were in fair to good condition, and cardiac failure, when present, was mild. All of the patients were ambulatory and were attending either the outpatient department of the University Hospitals or the private consulting room of one of us. Table IV gives the data on the 126 patients. The score range was from minus 3 to 17, with an average index of 10.05. The variation of scores may be judged by the standard deviation of 4.24 and the standard error of 0.3784. The distribution of these pathologic cases is contrasted with that of the normal controls in Table V. There was a remarkable parallelism, and this is graphically illustrated in Fig. 1. The patients with all types of cardiovascular dis-

ease behaved much the same as the large group of normals, although the normals skewed slightly to the right (slightly higher scores), and the abnormals skewed slightly to the left (slightly lower scores).

TABLE VI

HYPERTENSIVE CARDIOVASCULAR DISEASE

DISTRIBUTION OF SCORES	
NUMBER	SCORE
1	-1
3	3
2	4
1	5
1	6
2	8
5	9
3	10
5	11
5	12
2	13
4	14
3	16
Average	9.81
Standard deviation	4.05
Standard error	0.471

Hypertensive Cardiovascular Disease.—Thirty-seven patients with persistent hypertension were studied. The group included patients without heart failure, patients with moderate failure, and patients who were digitalized and not digitalized. The scores ranged from minus 1 to 16, with an average of 9.81. The failure group (all but one of whom were digitalized) ranged from 3 to 14, with an average of 10.0. The non-failure group scored from minus 1 to 16, with an average of 9.7. In other words, the average index in this group would be classed as "fair," with many cases falling in the "very good" and "excellent" groups (Table VI).

TABLE VII

ARTERIOSCLEROTIC HEART DISEASE

CASE	SEX	AGE	FAILURE	DIGITALIZED	INDEX
1	M	47	0	0	8
2	M	58	0	0	12
3	M	56	+	+	11
4	M	78	0	0 A. F.	9
5	M	46	0	0	15
6	M	41	0 Rt. B.B.B.	0	8
7	M	44	0	0	12
8	M	53	0	+	4
9	F	55	0	+	6
10	F	60	0	+	14
11	M	65	0	0 A. F.	15
12	M	52	0	0	11
13	M	61	0	+	4
	Range of scores			4 to 15	
	Average			9.92	
	Standard deviation			3.647	
	Standard error			1.81	

Angina Pectoris and Myocardial Infarction.—Thirteen patients with coronary arteriosclerosis and angina pectoris were studied (Table VII). The indices ranged from 4 to 15, with an average of 9.92.

TABLE VIII

MYOCARDIAL INFARCTION

DISTRIBUTION OF SCORES	
NUMBER	SCORE
1	6
2	7
3	8
1	9
2	11
2	12
2	13
1	14
1	15
1	16
Range of scores	6 to 16
Average	10.63
Standard deviation	3.016

Sixteen cases of old myocardial infarction in relatively young men are summarized in Table VIII. The index ranged from 6 to 16, with an average of 10.63. Four patients whose illness dated back only three months gave good scores.

TABLE IX

RHEUMATIC HEART DISEASE

DISTRIBUTION OF SCORES	
NUMBER	SCORE
1	-3
1	1
2	2
1	3
5	5
4	6
2	7
1	8
3	9
4	10
6	11
3	12
3	13
5	14
3	15
3	16
4	17
Range of scores	-3 to 17
Average	10.1
Standard deviation	4.736
Standard error	0.464

Rheumatic Heart Disease.—Fifty-one patients with rheumatic heart disease and severe valve lesions were studied (Table IX). The index

ranged from minus 3 to 17, with an average of 10.1. The patients with cardiac failure had scores ranging from 3 to 17 (average, 11.8), and the patients without cardiac failure had scores ranging from minus 3 to 17, with an average of 9.8. Digitalis made no appreciable difference in the score. The patients with combined aortic and mitral disease did equally as well as the patients with mitral stenosis alone. Patients with normal sinus rhythm and those with auricular fibrillation did equally well. In this group of fifty-one patients, thirty-four had a "fair" to "excellent" rating.

Auricular Fibrillation, Etiology Unknown.—Two male patients, aged 35 and 43 years, respectively, had chronic auricular fibrillation without any discoverable cause. They were both active; the first was a physician, the second, a crane operator. Their scores were 3 and 13, respectively.

Normal Mechanism.—The cardiac mechanism was normal in ninety-four cases. The scores ranged from minus 3 to 17, with an average of 9.9 (Table X).

TABLE X

NORMAL MECHANISM

	NUMBER	RANGE	AVERAGE
Aortic insufficiency (syphilitic)	2	11, 16	13.5
Arteriosclerotic heart disease	11	4 to 15	9.5
Coronary thrombosis	15	6 to 16	10.5
Hypertensive heart disease	33	-1 to 16	9.6
Hypothyroidism	1	12	
Leucemia and anemia	1	9	
Right bundle branch block	1	13	
Rheumatic heart disease	30	-3 to 17	9.5
Total	94	-3 to 17	9.9

Auricular Fibrillation.—In thirty-two cases of auricular fibrillation the index variation was from 2 to 17, with an average of 11.9 (Table XI).

TABLE XI

AURICULAR FIBRILLATION

	NUMBER	RANGE	AVERAGE
Arteriosclerotic heart disease	2	9, 15	12.0
Congenital heart disease	1	8	
Coronary thrombosis	1	12	
Hypertensive heart disease	4	9 to 16	10.3
Hyperthyroidism	1	4	
Idiopathic	2	3, 13	8.0
Rheumatic heart disease	21	2 to 17	10.5
Total	32	2 to 17	11.9

Patients With No Heart Failure.—In 102 cases there were no signs of congestive failure. Here the scores ranged from 2 to 17, with an average of 10.1 in the digitalized group, and from minus 3 to 17, with an average of 10, in the undigitalized group (Table XII).

TABLE XII

PATIENTS WITH NO HEART FAILURE

	DIGITALIZED			NOT DIGITALIZED			TOTAL		
	NO.	RANGE	AV.	NO.	RANGE	AV.	NO.	RANGE	AV.
Aortic insufficiency (syphilitic)	1	16					1	16	
Arteriosclerotic heart disease	4	4 to 14	7.0	8	4 to 15	11.3	12	4 to 15	9.9
Auricular fibrillation (idiopathic)	2	3, 13	8.0				2	3, 13	8.0
Coronary thrombosis	2	6, 12	9.0	14	7 to16	10.8	16	6 to 16	10.6
Hypertensive heart disease	2	9, 16	12.5	21	-1 to 16	9.4	23	-1 to 16	9.7
Hyperthyroidism; A. F.	1	4					1	4	
Hypothyroidism				1	12		1	12	
Leucemia and anemia				1	9		1	9	
Rheumatic heart disease	17	2 to 17	10.5	26	-3 to 17	9.3	43	-3 to 17	9.8
Right bundle branch block				1	13		1	13	
Tetralogy of Fallot; A. F.	1	8					1	8	
Total	30	2 to 17	10.1	72	-3 to 17	10	102	-3 to 17	10.0

Cardiac Failure.—There were twenty-three cases of mild congestive failure; all but one of these patients were digitalized. The index in the digitalized group ranged from 3 to 17, with an average of 12 (Table XIII).

TABLE XIII

CARDIAC FAILURE

	DIGITALIZED			NOT DIGITALIZED			TOTAL		
	NO.	RANGE	AV.	NO.	RANGE	AV.	NO.	RANGE	AV.
Aortic insufficiency (syphilitic)	1	11					1	11	
Arteriosclerotic heart disease	1	11					1	11	
Hypertensive heart disease	13	3 to 14	9.5	1	12		14	3 to 14	11.8
Rheumatic heart disease	8	3 to 17	11.8				8	3 to 17	10.0
Total	23	3 to 17	12.0	1	12		24	3 to 17	11.7

This study of 126 patients, 121 of whom had serious cardiac or hypertensive disease, frequently showed favorable Schneider indices. This emphasizes the contention of Schneider, Armstrong, and Scott that an unfavorable test alone must not disqualify, and, likewise, that a favorable result must be backed up with a careful history and physical examination. The Schneider index is frequently as favorable in persons with organic cardiovascular disease as in normal controls, and cannot be employed to differentiate normal from abnormal cardiovascular states. The limitations of the Schneider index have been emphasized. The test is most valuable for follow-up observations, for a lowering of the index signifies some variation in either the psychic or the physical condition.

CONCLUSIONS

1. As a test of physical efficiency of the cardiovascular system, the Schneider test makes very slight demand on the cardiovascular reserve.

2. The Schneider test is sensitive to both physical and psychic factors.

3. The Schneider index was obtained on ten digitalized normal controls. The index was lower in eight cases, unchanged in one case, and increased in one case. The reduction in the index was due to the slower return of the heart rate, after exercise, to the standing level.

4. Of 37 cases of hypertensive disease, the index was "excellent" in 7, "very good" in 12, "fair" in 8, and "doubtful" or "unsatisfactory" in 10.

5. In 13 cases of angina pectoris the indices ranged from "doubtful" to "very good."

6. Of 16 cases of remote myocardial infarction, the range was from "fair" to "excellent" in 10.

7. In 51 cases of rheumatic heart disease, 15 indices were "excellent," 12 were "very good," 7 were "fair," 3 were "doubtful," and 14 were "unsatisfactory."

We extend our thanks to Dr. Joseph Wearn for his stimulating interest in this study, and to the members of the resident medical staff of Lakeside Hospital who were the subjects of the digitalis experiments.

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ADDENDUM

Brouha and Heath recently published a paper (Brouha, Lucien, and Heath, Clark W.: Resting-Pulse and Blood Pressure Values in Relation to Physical Fitness in Young Men, New England J. Med. **228**: 473, 1943) showing that there was no satisfactory relation between basal pulse rate, sitting pulse rate, and physical fitness for strenuous exertion in normal, healthy young men, and that emotional factors are largely responsible for the high resting pulse rates that are commonly found during the preinduction medical examination of healthy young men.

BLOOD PRESSURE IN THE AGED

A Study of One Thousand Elderly Male Subjects

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THE realization that there are ever increasing numbers of aged persons in the United States has given fresh impetus to the study of geriatrics. In a period of forty years (1900-1940), during which the population of this country increased slightly more than one and one-half times, the number of persons 65 years old, or older, almost trebled (approximately 9,000,000). As this change in the age distribution of the population continues, the physician will be confronted more and more with the problem of the care of the aged and the diseases and infirmities arising from the senile state. For a clearer understanding of these problems, further study of the physiology and pathology of senescence and the establishment of normal standards for old age are essential.

Most statistics concerning the variations of blood pressure with age are based upon studies of comparatively young adults. In some series the number of senile subjects was too small to permit of accurate analysis of blood pressure trends in old age. In others, all elderly persons were classified as one homogeneous group under a designation such as "subjects over the age of 60," and no attempt was made to consider the respective age subdivisions of this group. Hence such studies contributed little to an understanding of the blood pressure changes in the latter decades of life.

The concept that blood pressure increases with the process of aging is so deeply rooted that the old formula "100 plus your age" is still universally applied by the laity, and is even today accepted by some physicians. That normal blood pressure does rise with advancing years, but much more slowly than the age, is suggested by the compilations of life insurance underwriters.[1, 2] Their tables indicate that, normally, the blood pressure of white men rises from 120/79 at the age of 20 years to 138/89 at the age of 65 years.

Bowes,[3] in a study of the average blood pressure of one hundred fifty aged subjects, observed a similar increase with advancing age. The systolic pressures of the men rose from 145 mm. in the 60- to 65-year-old group to 163 mm. in the 80- to 84-year-old group, and the pulse pressure increased from 63 mm. to 80 mm. in the same period.

Lewis,[4] in an analysis of blood pressure variations, observed that the greatest rise in systolic pressure occurred after the age of 65 years.

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His study, however, included only one hundred men, twenty in each decade from the age of 40 to 89 years. The average systolic pressure rose from 116 mm. in the 40- to 44-year-old group to 158 mm. in the 85- to 89-year-old group. The average diastolic pressure, on the other hand, showed little change in succeeding decades.

Miller's[5] study of eight hundred fifty-three men and one hundred twenty-eight women who were past middle age also showed that there is a rise in average systolic pressure with advancing years. At 50 to 54 years in the male group, the systolic level was 132 mm., and rose to 157 mm. in the 85- to 89-year-old group. The pulse pressure showed a corresponding rise from 46 mm. to 71 mm., whereas the diastolic pressure varied only slightly in the same interval (84 mm. to 87 mm.).

Although such observations seem to indicate that systolic pressure normally tends to increase with age, not everyone agrees that this is true. Alvarez and Stanley[6] have stated that a systolic pressure of 115 mm. is just as normal, and one of 140 mm. just as abnormal, for an old man as a young one. Similar views as to the constancy of normal blood pressure were expressed by Huber,[7] Faught,[8] and others.

Robinson and Brucer[9] have declared even more emphatically that the range of normal blood pressure must be considered "as immutable and as constant as the temperature and pulse rate." They point out that the average levels which were regarded as normal in previous studies were distorted by including abnormally high pressures. The authors maintain that, although elevated pressures rise with advancing years, normal levels remain unchanged. In their opinion, normal blood pressure does not exceed 120 mm., and levels of 130 mm. to 140 mm. can never be considered normal at any age. In their statistical study of more than ten thousand persons, the authors attempted to eliminate the abnormal pressures in order to arrive at a more accurate average of normal blood pressure. This was supposed to be accomplished by excluding subjects with a pressure in excess of 140/90, because, with this level as the upper limit of normal, the authors found no increase with age. As pointed out by Treloar,[10] this manipulation was actually a means of forcing a desired result. Although only 13.3 per cent of their male subjects were excluded by this procedure, it will be shown that, when aged subjects are taken at random, over 60 per cent would be affected by such a procedure. It is further to be noted that although 7,478 men were included in their entire group, only 189 were more than 65 years of age. Finally, the authors state that 120 mm., systolic, and 80 mm., diastolic, are the upper limits of normal blood pressure, and maintain that when these levels are exceeded there is an abrupt rise in death rate. That this does not hold for certain elderly persons who comprised an appreciable percentage of the entire group will be shown in this study.

It is evident, therefore, that little accurate information is available concerning blood pressure trends among persons over the age of 60 years. Furthermore, no attempt has previously been made to classify such subjects into blood pressure groups (normal, systolic hypertension, diastolic hypertension) and to study the incidence of each group in old age. It is realized that differentiation on the basis of blood pressure levels alone is purely arbitrary, but the value of such a classification, when it is correlated with life expectancy studies for the respective groups, is apparent.

For the purpose of this study an analysis was made of the blood pressure levels of one thousand male subjects, all of whom were retired seamen between the ages of 60 and 95 years. The age distribution of the group was fairly uniform throughout this period. The mariners were residents of Sailors Snug Harbor, an institution open to seafaring men who lack financial support, are unemployed because of the infirmities of old age, or are incapacitated by disease or injury. The majority of these men were of Scandinavian descent. Their social habits had been relatively uniform; almost all of them had used alcohol moderately or in excess. Most of the subjects had been exposed to diseases that are prevalent all over the earth. The nature of their former occupation and recreation differed sharply from that of the sedentary urban groups who have been analyzed in other studies. Inasmuch as these men may be regarded as of a relatively "pure strain" with respect to racial and environmental factors, and were otherwise unselected, they seemed ideal for a study of the relationship between arterial pressure and life expectancy.

The measurements were made during routine morning rounds, with a mercury manometer, by the auscultatory method. The level at the beginning of the fourth phase was taken as the diastolic pressure. Emotional factors were minimal, and the subjects were accustomed to having their blood pressure measured.

RESULTS

Table I shows the effect of age upon average blood pressure. The systolic rose from 147 mm. in the 60- to 64-year-old group to 160 mm. in the 85- to 95-year-old group. The pulse pressure increased from 65 mm. to 74 mm. over the same period. The diastolic pressure varied little after the age of 65 years.

TABLE I

AVERAGE BLOOD PRESSURE IN OLD AGE

AGE (YEARS)	NUMBER	SYSTOLIC	DIASTOLIC	PULSE PRESSURE
60-64	120	147	82	65
65-69	201	153	86	67
70-74	157	154	85	69
75-79	248	156	86	70
80-84	170	157	85	72
85-95	104	160	86	74

Table II shows the relation between age and blood pressure levels. All blood pressures below 150/95 were classified as *normal;* when the systolic and diastolic levels exceeded 150/95, *diastolic hypertension* was said to be present, whereas systolic pressures above 150 mm. with diastolic pressures under 95 mm. were regarded as indicative of *systolic hypertension.* It is seen that the percentage of "normals" decreased from 67 per cent in the 60- to 64-year-old group to 34 per cent in the 85- to 95-year-old group. Of the one thousand subjects, slightly less than half had blood pressures of 150/95 or less. The incidence of systolic hypertension rose progressively with age from 17 per cent to 38 per cent, and, of the entire group, more than one-quarter had this type of blood pressure elevation. On the other hand, the incidence of diastolic hypertension seemed to rise more slowly with age (16 per cent to 28 per cent), and those who manifested it comprised less than one-quarter of the entire group. Of the one thousand subjects, therefore, it can be said that approximately two in four were "normals," one in four had "systolic hypertension," and one in four had "diastolic hypertension." Actually, however, the commonest type of blood pressure elevation was systolic hypertension; it was present in more than one-third of all the subjects over the age of 75 years.

TABLE II

PERCENTAGE INCIDENCE OF NORMAL AND HIGH BLOOD PRESSURE LEVELS IN THE AGED (1,000 SUBJECTS)

AGE (YEARS)	60-64 (120)	65-69 (201)	70-74 (157)	75-79 (248)	80-84 (170)	85-95 (104)	60-95 (1,000)
NORMAL (496)	67	54	52	39	40	34	49.6
SYSTOLIC HYPERTENSION (276)	17	24	26	36	38	38	27.6
DIASTOLIC HYPERTENSION (228)	16	22	22	25	22	28	22.8

In Table III an analysis is made of the variations in "normal" blood pressure with age. It is seen that in the four hundred and ninety-six subjects in this class the average normal systolic pressure rose from 132 mm. in the 60- to 69-year-old group to 136 mm. in the 80- to 95-year-old group. It has been stated by others that this rise is not the result of changes in normal pressure (120 mm. or less), but shows that prehypertensive levels were included in the normal group. Nevertheless, in this study, the incidence of normal pressure (in the restricted sense) decreased with age, whereas the incidence of upper levels of normal showed a corresponding rise. This strongly suggests that, among elderly persons, all levels of normal systolic pressure tend to increase with advancing years. In sharp contrast, the average normal diastolic pressure decreased slightly with age, and the incidence of

low diastolic pressures increased concomitantly. The cause for these changes in normal pressure will be discussed under systolic hypertension.

TABLE III

ANALYSIS OF TRENDS IN NORMAL GROUP

(496 SUBJECTS)

AGE (YEARS)	SYSTOLIC				DIASTOLIC			PULSE PRESSURE
	AVERAGE (MM.)	110 OR LESS	120 OR LESS	140-150	AVERAGE (MM.)	70 OR LESS	90-95	
60-69	132	11%	30%	22%	78.3	35%	11%	54
70-79	134	8%	26%	30%	77.1	44%	12%	57
80-95	136	4%	20%	34%	76.0	48%	12%	60

On the assumption that the subjects of this study were a representative sample of the many who preceded them at Sailors Snug Harbor, an analysis of three hundred sixty-two consecutive deaths was undertaken, and the cases were classified according to blood pressure levels and age at death. By comparing the incidence of the various levels of blood pressure in the living with that of the same levels among those who had died, it was possible to relate expected and actual mortality (Table IV).

TABLE IV

LIFE EXPECTANCY IN THE AGED*

AGE	60-64	65-69	70-74	75-79	80-84	85-95	60-95
NORMAL	–10	–10	–15	–10	– 7	– 6	–10
SYSTOLIC HYPERTENSION	–18	– 8	0	– 6	– 3	–13	– 7
DIASTOLIC HYPERTENSION	+62	+36	+36	+24	+20	+25	+32

*Percentage variation from unexpected mortality.

DISCUSSION

Considerable interest has been aroused by the contention of Robinson and Brucer[9] that systolic pressure in excess of 120 mm. is "in the zone of hypertension," and that anything above this level is attended by an abrupt rise in mortality rate. Although this index of prognosis may be accurate for younger adults, the clinician has long been aware of its inadequacy in predicting life expectancy in the aged. As pointed out by Fineberg,[11] elevation of the systolic pressure, with a normal or low diastolic pressure, is found among aged persons who are comparatively free from the signs and symptoms of cardiovascular disease. The fact that this form of hypertension does not influence the health or life expectancy of the patient was commented upon more recently by Boas.[12] In this study it has been shown that such subjects make up a large percentage of the older groups. Previously, the idea that this type of blood pressure elevation is benign was based merely on

clinical impression, but additional support is furnished by the analysis in Table IV. The latter expresses actual mortality for the respective age-blood pressure groups in terms of percentage variation from expected mortality. The figures are based on the ratio of actual to expected deaths in each group. The expected mortality was derived from the incidence of the various blood pressure levels in the living subjects. The actual mortality was calculated from an analysis of three hundred sixty-two consecutive deaths prior to 1940. Comparison of these figures is believed justified in view of the uniformity of the groups under consideration. It is clear that the life expectancy of the subjects with systolic hypertension is strikingly similar to that of the subjects with normal blood pressure, but the prognosis of diastolic hypertension is very different. Consequently, life expectancy in the aged would seem to be definitely related to the diastolic blood pressure, rather than to the systolic.

Systolic hypertension in old age is commonly regarded as a consequence of diminished elasticity of the aorta and its large branches, and is usually associated with marked arteriosclerosis of these vessels.[13] As a result of loss of distensibility of the vessel wall, the arterial pressure becomes elevated above normal with each ventricular systole. At the same time, diminution in the elastic recoil of the aorta tends to produce a lowering of the diastolic pressure, with a further increase in the pulse pressure. This effect in some instances is counterbalanced by the widening and elongation of the aorta which are frequently observed in old age. Wiggers[14] is of the opinion that, in some cases, systolic hypertension may actually represent long-standing diastolic hypertension complicated by sclerosis and rigidity of the aorta. In fact, when the heart is enlarged it is generally impossible to exclude the possibility that diastolic hypertension may have been present previously in these aged subjects. On the other hand, the frequent association of a small heart and marked arteriosclerosis of the aorta, as well as the much more favorable life expectancy in this group, strongly suggests that systolic hypertension in most instances originates as such, and has its own distinct mechanism. Fahr and Davis,[15] furthermore, have shown that increased rigidity of the arterial system, without an associated decrease in internal diameter, does not impose an added burden upon the heart.

It is worthy of emphasis that "normal" systolic pressure increased with age, whereas "normal" diastolic pressure showed a tendency to fall. The alteration in blood pressure produced by arteriosclerosis, therefore, is manifested not only by an increased incidence of systolic hypertension with age, but also by changes in pulse pressure even in normal persons (Table III). Robinson and Brucer[9] admitted that they were unable to explain the rise in blood pressure that occurred with age in 10 per cent of subjects whose systolic levels were less than 120

mm. Study of the elderly subjects at Sailors Snug Harbor revealed an increase in "normal" systolic pressure with age, regardless of whether the upper limit of normal was taken as 150 mm. or any level below this figure. This rise in pressure was considerably less, however, than that for the group as a whole, obviously because in the latter there was an increasing incidence of hypertension with advancing age.

Robinson and Brucer[9] excluded from their study all patients with systolic blood pressures above 140 mm. They originally considered this as the upper limit of normal mainly because average blood pressure did not increase with age when higher levels were discarded. This eliminated only 13.3 per cent of their entire group, which included subjects from 15 to more than 80 years of age. As already mentioned, the number of elderly subjects in their series was relatively small. If such a procedure were applied to this study, in which all of the subjects were over sixty years of age, 64 per cent of the entire group would have been eliminated. A similar percentage would have been involved in the old age groups studied by Miller[5] and Willius.[16] Furthermore, if Robinson and Brucer's revised definition of normal blood pressure (120 mm. or less) were applied to these aged seamen, only 13 per cent of the entire group could qualify as normal!

In the light of present knowledge, it is impossible to accurately state at what level physiologic pressures merge into pathologic ones. If by normal pressure one means levels consistently compatible with a long and healthy life, then so-called systolic hypertension in the aged should be included in this category. In the elderly patient with a blood pressure of about 170/70, with no cardiac enlargement or other manifestations of cardiovascular disease, the combination of elevated systolic pressure and low diastolic pressure may be regarded as physiologic. Although there is increasing evidence that arteriosclerosis is a disease rather than a degenerative change, it cannot be denied that the process of aging may leave its mark upon the vessels as well as the hair, skin, skeleton, and other structures. The repeated stretching and recoil of the arterial wall and the inherent tendency for elastic tissue to deteriorate with age may be the factors which underlie systolic hypertension. At any rate, it is far more accurate to regard the latter as "normal" than to identify it with diastolic hypertension, as insurance statistics inadvertently have done.

Although it is suggested that a relatively high systolic pressure may be regarded as physiologic in old age, the reverse holds true for diastolic pressure. Although 64 per cent of the entire group had systolic pressures above 140 mm., only 30 per cent had diastolic pressures in excess of 90 mm. In the "normal" group the average diastolic pressure was only 77 mm. The average diastolic pressure for normals and systolic hypertensives combined (77.2 per cent of the entire group) was 78 mm. The average diastolic pressure for all the subjects was

85 mm. These data seem to support the view of Robinson and Brucer[3] that the upper level of normal diastolic pressure has in the past been set too high.

This study has dealt with the arteriosclerotic type of systolic hypertension. Among other causes for elevation of the systolic pressure, with normal or low diastolic levels, are hyperthyroidism, aortic insufficiency, and heart block. The latter conditions are obviously associated with increased mortality rates, so that their inclusion in a study of the arteriosclerotic type would greatly alter the life expectancy figures for this group. The fact that other studies have not made this differentiation may explain the poor prognosis often given to this form of hypertension.

SUMMARY AND CONCLUSIONS

A statistical analysis of the blood pressure levels of one thousand male subjects, all retired seamen between the ages of 60 and 95 years, is presented. The variations in blood pressure and the inferences drawn therefrom are as follows:

1. Average systolic pressure and pulse pressure increase appreciably with age, whereas average diastolic pressure shows little variation after the age of 65 years.
2. The incidence of "normal" blood pressure (150/95 or less) falls markedly with age. Less than half of the subjects fell in this group.
3. Normal systolic pressure shows an increase with age, regardless of whether the upper limit is set at 150 mm. or at any figure below this level. All levels within the range of normal seem to participate in this change.
4. Normal diastolic pressure shows a tendency to fall with age, and the number of subjects with low diastolic pressures (70 mm. or less) increases correspondingly.
5. Arteriosclerosis not only increases the incidence of systolic hypertension with age, but also produces an increase in pulse pressure among subjects with normal blood pressure.
6. More than one-quarter of all the subjects and more than one-third of those over the age of 75 years had systolic hypertension.
7. A study of the ratio of actual to expected mortality revealed that the life expectancy of those with systolic hypertension was of the same order as for those with normal pressure. Diastolic hypertension, on the other hand, carries a much more unfavorable prognosis.
8. The life expectancy in this group was related to the diastolic, rather than to the systolic, pressure.
9. The incidence of diastolic hypertension increases more slowly with age; it was found in less than one-quarter of the entire group.
10. Normal diastolic pressure, as well as average diastolic pressure, was comparatively low, and it would seem that the upper limit of normal has in the past been set at too high a level.

11. The clinical course and life expectancy of patients with systolic hypertension strongly suggest that the latter originates as such, and has its own distinct mechanism.

12. For practical purposes, the clinician may regard systolic hypertension in the aged as "normal." Future study of the nature of atherosclerosis may reveal that it is physiologic in old age.

13. Finally, if 120 mm. represents the "true" upper limit of normal at any age, only 13 per cent of this group could be classified as normal.

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THE COMBINED USE OF STROPHANTHIN-K AND DIGITALIS IN THE TREATMENT OF CONGESTIVE HEART FAILURE

A Preliminary Report

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THIS study was undertaken to ascertain the effects of the combined use of strophanthin-k and digitalis on patients with congestive heart failure, and to demonstrate the degree of effectiveness and safety of this treatment. Brams, et al.,[1] working with strophanthin alone, demonstrated that it was safe, and obtained therapeutic effects comparable to those of digitalis. The proper method of digitalization after the administration of strophanthin-k has never been satisfactorily established. Batterman, et al.,[2] combined the use of ouabain, which is closely allied to strophanthin-k, and digitalis, and gave six to eight cat units initially, followed by a maintenance dose. Preliminary observations convinced us that full digitalization was necessary to effect a maximum response. Consequently, the patients in this series were completely digitalized after the initial dose of strophanthin.

Strophanthin-k is a relatively new therapeutic agent, and is not to be confused with strophanthin-g, or ouabain. Strophanthin-k is an amorphous glycoside derived from *Strophanthus kombé;* strophanthin-g is a crystalline glycoside derived from *Strophanthus gratus.* The crystalline strophanthins have greater toxicity and, consequently, a smaller therapeutic range than the amorphous strophanthins.

When strophanthin-k is given intravenously it acts within a few minutes, and is almost wholly excreted within twenty-four hours. Digitalis, on the other hand, is slow in action, and its rate of absorption and excretion is prolonged. These properties of the two drugs constitute the rationale of their combined use, for, as the action of strophanthin begins to wane, the digitalis begins to exert its maximum effect, and becomes the cardinal therapeutic agent.

The cases selected for study included patients with acute or chronic heart failure, irrespective of cause, who had not previously received digitalis for a period of at least ten days. The symptomatic and supportive care was uniform, and consisted of rest in bed, sedatives, oxygen, ammonium chloride, and a soft, salt-free diet. In addition to clinical evidence of failure, the exact cardiac status was ascertained by measurement of the venous pressure and the recording of electrocardiograms

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TABLE I

PATIENT	DIAG.	AGE	RACE	SEX	INITIAL RATE AND RHYTHM	FINAL RATE AND RHYTHM	INITIAL V.P.	FINAL V.P.	INITIAL C.T.	FINAL C.T.	TOTAL STROPH. (MGM.)	TOTAL DIGITALIS (C.U.)	COMPENSATION		RESULTS AND REMARKS
													RT.	LT.	
J. A.	ASHD HHD	56	C	F	165 (F)	94 (F)	27	10	--	--	0.25	19	3	4	Died in uremia. Had fully compensated
E. B.	ASHD	76	C	M	93 (F)	68 (F)	31	7	--	--	0.25	20	3	4	Discharged fully compensated
A. G.	ASHD	46	W	M	145 (F)	75 (R)	28	7.5	32	--	0.25	18	2	5	Discharged fully compensated
R. H.	HHD	63	W	M	102	88	13	7.5	25	--	0.25	22	1	4	Discharged fully compensated
M. J.	SHD	38	C	M	103	88	29	--	22	--	0.25	--	--	--	Failed to compensate. Aortic aneurysm compressing pulmonary artery
O. M.	ASHD	70	C	M	170 (F)	82 (F)	--	10.5	--	--	0.25	20	3	13	Discharged fully compensated
A. M.	THD	38	C	F	112	74	23	4.5	--	--	0.25	13	2	3	Discharged fully compensated
E. P.	HHD	33	W	F	102	86	24	10.5	--	--	0.25	14	3	5	Discharged fully compensated
W. T.	ASHD	53	C	M	112	--	--	--	--	--	0.25	--	--	--	Died. Coronary occlusion, femoral and cerebral emboli
O. W.	ASHD	71	C	M	88	72	24	10	--	--	0.25	22	3	6	Discharged fully compensated
D. R.	ASHD HHD	68	C	M	96 (F)	72 (F)	22	6	45	--	0.25	16	3	5	Discharged fully compensated
N. T.	HHD	42	C	F	126	96	27	8.5	32	14	0.25	20	3	3	Discharged fully compensated
C. T.	SHD	27	C	M	103	80	30	8	32	17	0.25	24	6	8	Discharged fully compensated
C. T.	SHD	27	C	M	106	75	25	10.5	30	14	0.25	12	3	3	Discharged fully compensated
E. W.	ASHD HHD	62	C	F	87 (F)	81 (F)	25	10.5	22	17	0.25	20	3	3	Discharged fully compensated
G. C.	ASHD HHD	68	C	M	75	75	27	13.5	30	15	0.25	21	4	4	Discharged fully compensated
M. W.	ASHD	58	C	M	106	70	29	10.5	34	18	0.25	24	6	16	Discharged fully compensated
R. M.	ASHD HHD	74	C	M	93	78	22	7	42	11	0.25	12	2	2	Discharged fully compensated

F—auricular fibrillation; R—normal rhythm; V.P.—venous pressure; C.T.—circulation time; c.u.—cat unit; ASHD—arteriosclerotic heart disease; HHD—hypertensive heart disease; SHD—syphilitic heart disease; THD—thyrotoxic heart disease.

in all cases. Decholin circulation time measurements also were obtained in the last seven cases; they were made before, and at daily intervals after, the institution of treatment.

Once the cardiac status was known, the patient was given, intravenously, 0.25 mg. of strophanthin-k, diluted with 10 c.c. of physiologic saline, over a period of three minutes. Slow administration was employed in order to allow complete fixation of the drug by the myocardium. Immediately, six to nine grains of digitalis leaf were given orally, followed by three grains three times a day until the patient was digitalized. A close record was kept of subjective improvement and signs of toxicity.

The criteria of recovery from heart failure consisted of disappearance of dyspnea, râles, cyanosis, and edema, diminution in the size of the liver, and return of the venous pressure and circulation time to normal. Electrocardiograms, which were taken daily, offered objective evidence as to the effect on the myocardium and conduction mechanism.

Eighteen patients were studied, fifteen of whom were completely relieved of their heart failure. Two of the patients died, one of uremia, and the other of peripheral and cerebral emboli eight days after coronary occlusion. Both of these patients, however, had recovered from heart failure prior to death. One patient with an aortic aneurysm compressing the pulmonary artery failed to respond.

Fifteen of the patients were colored and three were white; thirteen were males and five were females. The ages ranged from 27 to 76 years, averaging 53.8 years. There were six cases of pure arteriosclerotic heart disease, three of hypertensive heart disease, five of combined hypertensive and arteriosclerotic heart disease, three of syphilitic heart disease, and one of thyrotoxic heart disease.

The average time required for the right side of the heart to compensate was 3.1 days, and, for complete compensation, 5.5 days.

The total amount of strophanthin-k given to each patient was 0.25 mg.; the total amount of digitalis required for digitalizing each patient ranged from 12 to 24 cat units, averaging 18.5 cat units.

All patients noticed subjective improvement within the first two to six hours; this was progressive, and closely paralleled objective signs of improved cardiac function. There were practically no untoward toxic manifestations, aside from the nausea and occasional vomiting associated with full digitalization. Electrocardiograms failed to show any detrimental effects on the conduction mechanism or on the state of the myocardium.

The heart rate was not strikingly altered during the first six to twelve hours, although there was a uniform and progressive slowing of the pulse rate. The rhythm remained unchanged in all cases of sinus rhythm. Six patients had auricular fibrillation, one of whom recovered normal rhythm; this patient's auriculur fibrillation had been present for two

months, and followed thyroidectomy. The absence of definite and more immediate bradycardia suggests the possible necessity of giving a larger initial dose of strophanthin-k.

The rapidity of recovery, particularly of the right side of the heart, was the most striking and dramatic feature. Both clinical and objective observations demonstrated the effectiveness of the combined use of strophanthin-k and digitalis in this respect. It is our belief that full digitalization after giving strophanthin played a major role in effecting this rapid result.

CONCLUSIONS

1. The use of strophanthin-k and digitalis in combination is safe and efficient.

2. Full digitalization after giving strophanthin is essential.

3. Patients with congestive heart failure usually recover rapidly when this form of therapy is used.

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AORTIC REGURGITATION CAUSED BY DILATATION OF THE AORTIC ORIFICE AND ASSOCIATED WITH A CHARACTERISTIC VALVULAR LESION

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THERE are occasional references to aortic regurgitation unaccompanied by structural changes in the aortic valve leaflets.[1] It is known as "functional" aortic insufficiency, and is generally attributed to dilatation of the aortic ring. Arteriosclerosis,[2] hypertension,[3] and chronic nephritis[4] have been regarded as important factors in the pathogenesis of this type of aortic valvular insufficiency. The subject, which has always been controversial, received greater attention in previous years than it does at present. Nevertheless, Garvin[5] recently reported fourteen instances of this unusual cardiac condition in a series of two hundred hypertensive patients.

There are cases of aortic regurgitation which are not easily classified because of certain clinical peculiarities. We refer to patients over the age of 50 years, usually near or past 60 years, and usually men, in whom the evidence for syphilitic infection is slight or nonexistent. Neither the history nor the physical examination indicates the presence of subacute bacterial endocarditis. Predominant aortic regurgitation of rheumatic origin is, of course, rare at this age, and can usually be excluded after brief consideration. The diastolic aortic murmur may or may not be transmitted down along the left sternal border, as in all types of aortic regurgitation, but in these elderly patients the transmission is frequently limited over a small area, in spite of the prominence of the murmur. The murmur may be loud and harsh, and is often fused with, or engrafted upon, an accentuated aortic second sound. Its physiologic significance may be questioned because the blood pressure changes and peripheral signs characteristic of aortic regurgitation are usually only moderately developed, and sometimes barely detectable. The systolic pressure in some cases is high enough (200 mm., or more) to indicate per se the existence of hypertension. The diastolic pressure is often higher than in the ordinary types of aortic regurgitation, occasionally ranging as high as 100 mm. It seldom falls below 50 mm.; so-called zero diastolic readings are rarely, if ever, recorded. A Corrigan pulse is present, but generally it is not as striking as in cases of well-developed aortic regurgitation of infectious origin. The other classical signs of aortic regurgitation are usually absent. We have not encountered a capillary pulse, a Duroziez murmur, or a Traube pistol shot sound.*

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*We have no experience in eliciting Loewenberg's[6] sign of functional aortic valvular insufficiency, namely, the absence of a much higher systolic blood pressure in the legs than in the arms.

In six of the eleven cases on which this report is based the diastolic murmur was preceded by a short systolic aortic murmur, and, in one instance, there was a systolic thrill in the aortic area. The diastolic murmur was the striking physical sign in all cases.

Our interest in so-called functional aortic regurgitation was aroused by (1) our observation of elderly patients who appeared to have aortic regurgitation which we hesitated to designate as syphilitic because of their repeatedly negative blood Wassermann and Kahn reactions, and (2) by our observation at necropsy, in such cases, of changes in the aortic leaflets which were different from the ordinary lesions of syphilis, rheumatic fever, and atherosclerosis.

Fig. 1.—Case 2. Various types of central, free-marginal sclerosis, enlargement of the sinuses of Valsalva, dilatation of the aortic ring, and widening of the commissures by separation of the leaflets, in an aged, hypertensive patient with non-syphilitic aortic regurgitation. Note irregular thickening and lipping of the endocardium in the mid-portion of the posterior (middle) leaflet. The posterior sinus is enlarged. The right anterior sinus (*R*) is ballooned by cotton; the corpus arantii of the right leaflet has disappeared; the mid-portion of the free margin of the leaflet shows a crescentic indentation and is indurated; the process is terminated on each side by a bicornate sclerotic projection (small arrows). The left anterior leaflet shows a small, central, rodlike thickening of the free margin, 0.8 cm. long. The lateral portions of all leaflets are normally delicate, but somewhat elongated. They have been stretched apart, leaving a furrow at the third commissure (*X*). There is no calcium or atheroma in this aortic valve and scarcely any atheromatosis in the aortic arch.

This lesion is a sclerotic thickening confined to the mid-portion of the free edge of the aortic leaflets. It is essentially a loss and a fibrous replacement of the original corpora arantii, without involvement of the lateral portions of the free margin of the leaflet or of the body of the leaflet, except insofar as marked central involvement necessarily extends some distance toward the periphery. In some instances, the sclerotic thickening may extend from the mid-point almost throughout the entire length of the free edge of the leaflet. The commissures are not involved, except occasionally in a peculiar way, as indicated later.

This lesion in the mid-portion of the free margins may assume odd shapes and attain considerable size. All three leaflets are usually involved. The central thickening may appear as a bicornate projection, with two sclerotic tips or nodules enclosing a central sector where the valvular substance has been eroded (Fig. 2). The lesion is firm, densely sclerotic, and without resemblance either to the original corpus arantii or to verrucae. In some cases there is a rolled thickening or lipping of the free margin, most pronounced at the mid-point, and gradually tapering off into the delicate normal structure at the lateral portions of the leaflets (Fig. 4). The bicornate and the lipped thickenings are the common types of deformity. Rarely, central lipping progresses to eversion of an entire leaflet, as in the "hinge valve" lesions of aortic insufficiency.[7, 8] Also rarely, there is a buttonlike thickening or a shield formation over the site of the original corpus arantii. In some cases the three leaflets show different deformities; one may have central hornlike projections, the others be lipped or rolled in varying degree.

Fig. 2.—Case 4. The "bicornate" sclerotic lesions replace the corpora arantii of the aortic leaflets. Syphilitic aortitis is present, but does not involve the commissures. The lateral portions of all three leaflets remain normally delicate. Cotton partially balloons out the sinuses.

The hard, often calcific, roughening of the corpora arantii in the hypertrophied hearts of elderly men who had systolic aortic murmurs suggestive of aortic stenosis should not be confused with the central deformity of the leaflets herein described.

The central, free marginal fibrosis is one of a trio of changes characteristic of "functional" aortic regurgitation. The others are dilatation of the aortic ring, and enlargement in length and depth of the sinuses of Valsalva, with corresponding elongation of the aortic leaflets.

In most instances, as was pointed out by Osler,[2] the aortic ring is dilated; in our cases its circumference ranged from 7.5 to 10.5 cm.* In

*Osler's criteria require slight revision in the light of modern necropsy observation, as indicated by Roessle and Roulet.[9]

two of our eleven cases this could not be definitely established, for the circumference of the ring did not exceed 7.5 cm. However, dilatation of the root of the aorta, including the sinus area, was present in all eleven cases. Although, in most instances, this was merely continuous with the dilatation of the aortic ring, it sometimes was strikingly abrupt, i.e., the proximal portion of the ascending arch was engaged in a saccular, onion-shaped dilatation, resembling an aneurysm. Of course, no aneurysm in the true pathologic sense was present. With this supravalvular dilatation, the aortic sinuses were enlarged and the aortic commissures were drawn outward, so that they were located on an aortic circumference as much as 4 or 5 cm. in excess of the aortic ring circumference. This was the situation in the two cases in which the aortic ring circumference was considered to be within normal limits; the aortic leaflets were elongated to cover the enlarged aortic lumen. Eventually they became incompetent.

Fig. 3.—Case 4. Same as Fig. 2, but enlarged to show more clearly the normal commissures and the bicornate lesions. Half of the left anterior leaflet, its sinus, and the adjacent aorta have been cut away. Commissure 3 is also missing.

It was clear, therefore, that aortic insufficiency existed in the entire group; in most instances it was secondary to dilatation of the aortic valvular ring, but occasionally to supravalvular aortic dilatation that involved the sinuses. In view of this, and in the absence of typical valvular lesions of rheumatic and syphilitic heart disease, we tentatively spoke of this type of aortic insufficiency as "mechanical regurgitation."

As mentioned above, the sclerotic thickening of the valve leaflet did not extend into the commissures. However, we noted in some cases that the commissural junction, which normally is little more than a point

reached by the two adjacent portions of adjoining leaflets, was widened, not by fibrosis and edematous swelling, as is so often the case in syphilitic valvulitis, but by a pulling apart of the adjoining margins of the leaflets. The free margins in their lateral portions remained normally sharp-edged and appeared, if anything, lengthened, but the commissural junction became an actual space 2 or 3 mm. wide; it consisted of a depression without scarring, and resembled a furrow created by the tearing of normal attachments (Fig. 1). When this situation existed, there was an associated valvular insufficiency of marked degree.

Fig. 4.—Case 3. Central thickening along the free margins of the aortic leaflets, with normal commissures. No evidence of syphilis. Close inspection (aided by hand lens) of the right anterior leaflet (*R*) reveals early notching of the central, free-marginal lesion. The posterior (middle) leaflet shows more extensive sclerotic lipping of the free margin. Note slight degree of arteriosclerosis in the aorta.

The central marginal lesions occasionally occur in aortic leaflets which are the seat of lateral fenestrations. These fenestrations ordinarily do not cause aortic regurgitation, for they are above and beyond the line of closure of the leaflets. Rare exceptions have been recorded, but without unusual valvular lesions.[3, 10] We have seen, at necropsy, definite fibrous central thickening of the leaflets (Fig. 5); the thickening extended laterally along the lower border of the fenestration. The aortic ring in such a case is markedly dilated.

"Mechanical regurgitation" and syphilis are not infrequently associated. Some hypertensive patients with moderate aortic regurgitation, similar clinically to the type herein discussed, have a positive blood Wassermann reaction. The valvular insufficiency may remain surprisingly stationary or sometimes be intermittent, thus presenting an interesting problem. Hypertension might be expected to accelerate the rapid course of syphilitic aortic regurgitation.

We have seen patients with aortic regurgitation who at necropsy had syphilitic aortitis, but did not have the classic lesion of syphilitic aortic regurgitation, namely, widening and scarring of the valvular commissures. In some cases "commissuritis" was entirely absent, and, in others, so slight as to be insignificant. The leaflets did not show the characteristic shrinkage and retraction. The only obvious valvular lesion associated with the regurgitation was a sclerotic, bicornate thickening or lipping of the mid-portion of the free margins of the leaflets. Regardless of whether this was prominent or only moderately developed, the aortic ring was dilated and the sinuses were enlarged.

Fig. 5.—This case is not included in the series herein reported because of the obvious extension of syphilitic aortitis into two of the commissures, *A* and *C*. Commissure *B* is also widened, but stretching by dilatation of the aortic ring may have been a factor. The lateral portions of each leaflet are delicate, showing no marginal extension of sclerosis. The lateral fenestrations remain unchanged. The central portion of each leaflet is thickened; the corpora arantii are replaced by (1) a shield in the right anterior and the posterior leaflets, and (2) a bicornate lesion in the left anterior leaflet. The aortic ring is widened (circumference, 10.0 cm.), and there is even greater widening of the root of the aorta. From a case of syphilitic heart disease, with inconstant aortic regurgitation; the murmur disappeared and reappeared over a period of six years.

Three of our eleven patients had positive blood Wassermann reactions. At necropsy, two of these had syphilitic aortitis without commissural lesions. The third patient showed no gross evidence of aortitis or commissural involvement. Other cases have not been included in our series because there was undoubted extension of the syphilitic process into one, or possibly two, commissures. However, the dilatation of the aortic ring and the characteristic central marginal lesions were so outstanding as to indicate that, even with commissural thickening, the aortic regurgitation was the result of more than one factor (see Fig. 5).

Although aortic regurgitation which is associated with a positive Wassermann reaction must nearly always be considered syphilitic, it is apparent that, in occasional cases, the pathologic process is not typical. This probably accounts for the prolonged and atypical clinical course exhibited by some patients.

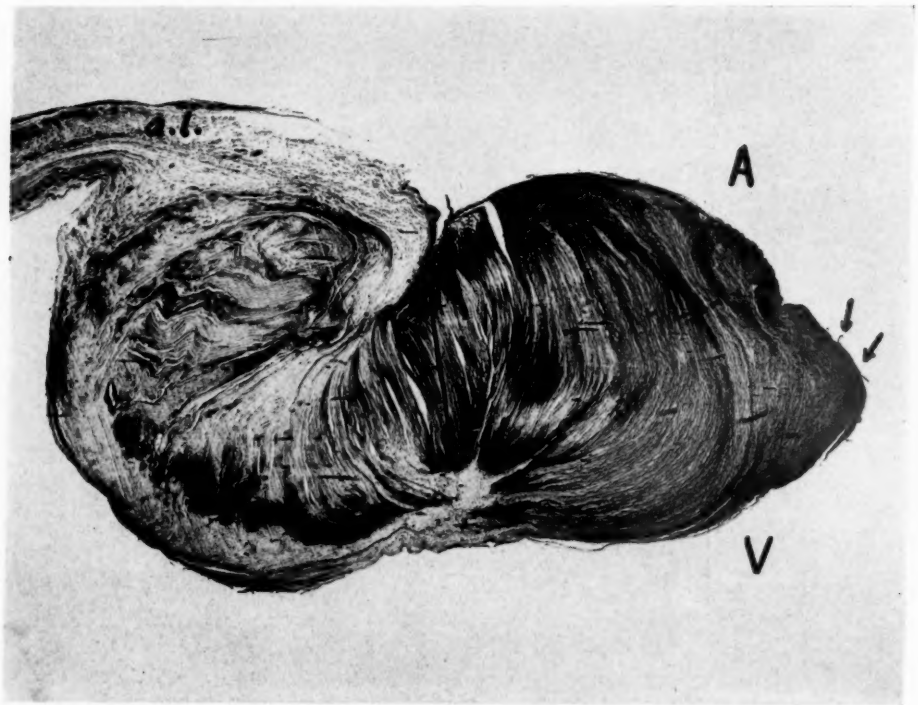

Fig. 6.—Case 4. Central, free-marginal sclerosis of aortic leaflet in "functional" aortic insufficiency. Section of a bicornate lesion (×15), showing dense, ovoid, nodular thickening attached to the end of a normal aortic leaflet (*a.l.*). In the latter, the original zonal structure is well maintained, and is free of vascularity or cellular infiltration. In only a small area at the extreme end of the nodule (marked by arrows), facing the aortic channel (*A*), is there a subendocardial cellular (histiocytic) infiltration. It is not visible in this low-power magnification. Ventricular surface (*V*); Weigert elastic stain.

Histologic Features.—Microscopic examination of the aortic leaflets showed that the valvular sclerosis was generally limited to the midportion of the free margins. Whatever lateral extension occurred progressed along the free margins; otherwise, the body of the leaflet remained normal down to its origin at the valvular ring. The division of the leaflet structure into generally well-defined zones—ventricularis, spongiosa, and fibrosa[11]—was not distorted or obscured by inflammatory or degenerative changes (Figs. 6 and 7). The absence of vascularity and of focal cellular infiltration throughout the length of the leaflet suggested that the fibrous lesion at the site of the corpus arantii was not caused by chronic endocarditis of the rheumatic type. In the occasional case in which syphilitic aortitis was present, the preservation of the normal valve leaflet was a strongly contrasting feature.

Vertical section through the central part of the leaflet usually revealed the central lesion at the free margin as a round, sometimes ovoid-shaped, nodule of dense fibrotic tissue. In some cases the appearance of the nodule suggested that it was the result of repeated concentric lamination of thrombotic material, long since hyalinized. The acellularity was striking except at the extreme distal end and for a short distance on the aortic aspect of this extremity. Here there was a small number of histiocytes and fibroblasts beneath a slightly roughened, occasionally broken, endocardial surface. Scarcely any deposition of fibrin was noted in numerous serial sections. A very small area of progressive inflammation was apparent at the most distal part of the lesion, in contrast to the normal state along the length of the leaflet. This small area faced the aortic, rather than the ventricular, aspect, which differentiated it from verrucae of infectious origin, and suggested that pressure was exerted from above downward, rather than from the ventricular direction.

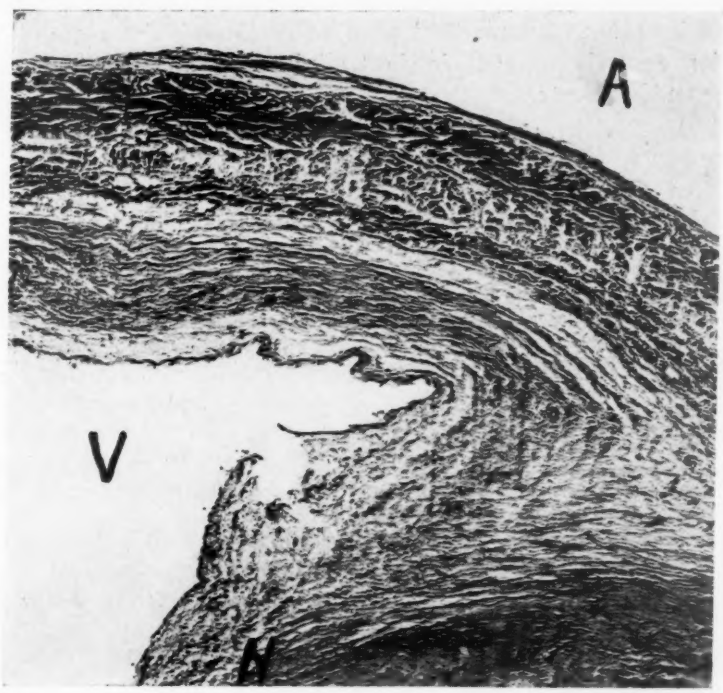

Fig. 7.—Case 4. Same as Fig. 6 (×42), showing free-marginal sclerotic nodule (*N*) at the end of a normal aortic leaflet. (*A*) Aortic aspect; (*V*) ventricular aspect. Weigert elastic stain.

Additional Clinical Data.—Ten of our eleven patients were men. There were six white patients and five Negroes. The youngest, and the only woman in the group, appeared much older than her stated age of 45 years. Nine of the remaining ten patients were 60 years of age or more; the oldest was 72 years.

Most, if not all, of these patients, including those with positive Wassermann reactions, had hypertension. Few eye-ground examinations were recorded, but the age of the patients, their usually elevated systolic blood pressure, and, finally, the pathologists' notes indicated that benign hypertension was the common cause of the "mechanical" aortic regurgitation.

The systolic blood pressure varied from 150 to 190, and the diastolic, from 35 to 100 mm. In nine of the eleven cases the diastolic pressure ranged from 50 to 75 mm.; a high diastolic pressure, i.e., 100 mm. or more, which has been reported as not infrequent by other observers,[4, 5, 12] was noted in one of our patients.

These patients died of circulatory failure. Dyspnea, basal pulmonary congestion, and edema of the legs were features common to all. Precordial pain was present in two cases. Although the majority did not survive their first attack of congestive failure, others gave a history of recurring attacks; one patient survived for six years. It is likely that these patients have the physical signs of aortic valvular disease for a much longer period than their short clinical course after the onset of failure would indicate.

Auricular fibrillation was present in five of the eleven cases.

The following are brief clinicopathologic notes on five cases.

CASE 1.—H. H., a laborer, aged 66 years, was admitted to the Philadelphia General Hospital June 26, 1937, on the service of Dr. Henry Jump, with cardiac decompensation. He had been well until one month before, when he noticed increasing shortness of breath and edema of the legs. His past medical history was unimportant. He had seven children and denied any history of venereal disease.

Examination revealed a well-nourished colored man, with normal pupillary reactions. The bases of both lungs were filled with râles, the liver was enlarged, and edema of the legs was present. The blood pressure was 155/60. The heart was moderately enlarged, especially to the left, and auricular fibrillation was present. There was a double aortic murmur, consisting of a short systolic, and a predominant, blowing, diastolic murmur. The latter was transmitted down along the left border of the sternum.

The electrocardiogram revealed inversion of T_1 and T_2 and a slurred QRS, in addition to auricular fibrillation.

The laboratory data included negative blood Kahn and Wassermann reactions and a blood urea nitrogen of 40 mg. per cent.

Death resulted from progressive cardiac failure on July 14, 1937. The clinical diagnosis was syphilitic aortic regurgitation and heart failure.

Necropsy (Dr. Merrill) revealed marked hypertrophy and dilatation of the left ventricle. The heart weighed 700 grams. The myocardium was firm, deep red, and 23 mm. thick in the upper lateral portion of the left ventricle. There was considerable dilatation of the aortic ring. The aortic valve circumference was 8.5 cm., the pulmonic, 8.0 cm., and the mitral, 11.5 cm. The aortic leaflets showed rolling and bicornate thickening at the central portion of the free margins. The bodies of the leaflets were practically normal, as were the commissures. No evidence of syphilitic aortitis was noted. There was slight thickening along the free margin of the mitral leaflet, apparently not rheumatic in origin.

Summary.—Hypertensive heart disease; hypertrophy and dilatation, especially of the left ventricle; and aortic insufficiency of the "mechanical" type.

CASE 2.—C. I., a white man, aged 70 years, was seen by one of us (E. S.) on Jan. 1, 1933, in the Paul Kimball Hospital, at Lakewood, N. J. The patient had a sudden attack of dyspnea which was a repetition of similar, but milder, attacks that had been occurring for several months. Examination revealed auricular fibrillation and a diastolic murmur at the third left intercostal space. The blood pressure was 175/80. The blood Wassermann reaction was negative. Fluoroscopic examination revealed enlargement of the left ventricle and a prominent aortic knob. The patient was discharged Jan. 9, 1933, with a diagnosis of hypertensive cardiovascular disease, but was readmitted Feb. 2, 1935, because of recurring dyspnea. The physical signs were as previously noted. The diastolic aortic murmur was pronounced, but limited to the third left intercostal space close to the sternum. The blood pressure was 160/45 and the pulse was of the Corrigan type. The patient left the hospital, improved, on March 19, 1935. It was decided later that syphilis was the probable cause of the aortic regurgitation, and, beginning in May, 1935, the patient received bismuth injections weekly for two months.

He was rehospitalized Nov. 19, 1935, because of circulatory failure; at this time the blood pressure was 138/45. The blood Wassermann and Kahn tests were again negative. Death occurred Dec. 12, 1935.

Necropsy revealed that the heart weighed 560 grams. The left ventricle was hypertrophied and dilated. The aortic valve was 7.8 cm. in circumference, the mitral, 10 cm., the tricuspid, 11.5 cm., and the pulmonic, 8.5 cm. Each aortic leaflet showed a central thickening of the free margin, consisting of irregular endocardial sclerosis. This was most pronounced in the posterior leaflet, where it extended along the free margin for 2.0 cm., and it spread down on the adjacent undersurface of the leaflet for 0.5 cm., forming a hard, protruding lip (Fig. 1). The central thickening of the right anterior leaflet was less prominent, but was marked by a small bicornate protuberance. In the left anterior leaflet the central lesion was a short, horizontal, rod-like thickening, 0.8 cm. long. The lateral portions of the free margins were normally delicate throughout. Commissure 3, the junction point of the adjacent portions of the posterior and left anterior leaflets, was widened, not by swelling or scarring, but apparently by a slight depression, suggesting that the lateral portions of the adjoining leaflets had been pulled away from each other. There was no calcific or sclerous thickening (arteriosclerosis) at the base of the aortic leaflets. Likewise, there was very little atheromatous or sclerotic degeneration in the aortic arch.

CASE 3.—C. M., a colored woman, who said she was 45 years of age, but appeared much older, was admitted on the service of Dr. D. Riesman, Sept. 10, 1935, complaining of shortness of breath and swelling of the legs and abdomen of three months' duration.

Examination revealed prominence of the neck veins and a blood pressure of 160/75. The heart was enlarged to the left; the apex was palpable beyond the midclavicular line in the fifth intercostal space. A loud, basal, diastolic murmur was heard behind the upper part of the sternum; its transmission was limited to the third left intercostal space.

Basal pulmonary congestion, hepatic enlargement, and edema of the legs were present and remained unaltered despite rest in bed and digitalization.

A Corrigan pulse was present, but no other peripheral signs of aortic regurgitation were noted.

The blood Wassermann reaction was negative. Death occurred Sept. 19, 1935. The clinical diagnosis was syphilitic heart disease with aortic regurgitation.

Necropsy (Dr. J. P. Welty) revealed that the heart weighed 400 grams and was transversely dilated. Section showed a soft, red myocardium, and a small, recent, myocardial infarct at the apex. Each aortic valve leaflet revealed thickening and lipping in the central portion of the free margin. The lipping was rounded in the right and left anterior leaflets, and gradually disappeared laterally into the normally delicate free margin. In the right leaflet this swelling was slightly eroded exactly in its center, giving rise to an early bicornate formation (Fig. 4). The posterior leaflet showed a larger and more irregular type of central thickening and lipping. There was no evidence of syphiltic aortitis.

CASE 4.—C. I., a white man, a merchant, aged 50 years, entered the Philadelphia General Hospital May 13, 1934 on the medical service of Dr. Thomas Klein, complaining of precordial pain and dyspnea, each of one month's duration. The patient noted palpitation and some edema of the ankles shortly before admission.

Examination revealed pulmonary basal congestion and congestive enlargement of the liver. The blood pressure was 180/35. The heart was enlarged to the left. There was a double aortic murmur, but the diastolic murmur was predominant. Numerous extrasystoles were present.

Urinalysis showed a cloud of albumin and numerous hyaline casts. Death was preceded by progressive azotemia. The blood Wassermann reaction was strongly positive.

Necropsy (Dr. Ingleby) revealed that the heart weighed 550 grams. Both ventricles were dilated, and the left was also moderately hypertrophied. Section revealed a rather soft myocardium without gross lesions. The coronary vessels were normal throughout. The aortic valve leaflets showed a striking deformity, namely, sclerotic thickening along the mid-portion of each free margin which had replaced the corpora arantii. It was a horizontal, cylindrical thickening, about 1.5 cm. long, with lateral bicornate projections (Figs. 2 and 3). The lateral portions of each leaflet were normally delicate, and the commissures were also normal, despite the adjacent development of syphilitic aortitis. The central, free marginal lesions were very firm. Their size, consistency, and shape were not those of ordinary verrucae. The aortic valve circumference was 8.6 cm., the mitral, 11.0 cm., the pulmonic, 8.2 cm., and the tricuspid, 13.0 cm.

The mitral valve was normal, as were the other valves.

Summary.—Left ventricular hypertrophy and dilatation; aortic regurgitation without commissural involvement; dilatation of the aortic ring; syphilitic aortitis; central free marginal sclerosis (bicornate lesions of "mechanical" regurgitation).

CASE 5.—J. M., a colored man, aged 66 years, was admitted to the Philadelphia General Hospital March 9, 1936 on the service of Dr. E. Eliason for hemorrhoidectomy. He was aware that he had high blood pressure and "heart trouble," but could give no approximate date of onset. He had sharp precordial pain, especially at night, accompanied by dyspnea. Edema of the ankles in the evening had been present for ten months. He was a laborer, and had seven children, all in good health.

His blood pressure was 208/80 and 225/80 in the left and right arms, respectively. There was marked cardiac enlargement both to the left and right. A systolic thrill was palpable at the base of the heart, and a rough systolic murmur in this area was transmitted to the vessels of the neck. It was followed by a loud, slapping diastolic murmur which was transmitted to the third and fourth left intercostal spaces. At this time the cardiac rhythm was normal. A Corrigan pulse was noted.

There was no evidence of congestive heart failure. The blood Wassermann and Kahn reactions were negative. Fluoroscopic study showed marked enlargement of the left ventricle and a greatly widened aortic arch.

The patient was readmitted to the medical service of Dr. S. Loewenberg, June 20, 1940, with paroxysmal dyspnea and cardiac decompensation. He had auricular fibrillation and signs of aortic valvular disease, as outlined above. The serologic reactions were again negative. He was readmitted Oct. 30, 1940, with recurring decompensation. His blood pressure then was 180/70. Attacks of substernal pain were relieved by nitroglycerin. Systolic and diastolic thrills were again palpable over the base of the heart, and a double aortic murmur was heard; the diastolic murmur was strikingly harsh and prolonged. The Wassermann reaction remained negative.

On his sixth and final hospitalization (service of Dr. Wm. Leaman, May 3, 1941) the blood pressure was 180/60. The physical signs were unchanged. On each previous admission the diagnosis had been syphilitic heart disease with aortic regurgitation. The diagnosis now became doubtful because the serologic tests for syphilis had been consistently negative, and because the survival period was rather prolonged. Digitalization was of no avail, and the patient died of congestive failure on June 9, 1941.

Necropsy (Dr. Conforth) revealed marked hypertrophy of the left ventricle. The heart weighed 700 grams. The myocardium was firm, 28 mm. thick in the upper part of the left ventricle, and revealed no focal scarring or necrosis. The coronary arteries were patent throughout, showing little sclerosis. The aortic valve leaflets were enlarged because of marked dilatation of the root of the aorta. The central portions of the free margins of the leaflets were thickened and lipped. The right aortic leaflet, in addition, was everted almost its entire length. Commissures 1 and 2 were normal; in 3 the component leaflets (posterior and left anterior) were about 2 mm. apart, evidently having been pulled away from each other. There was no evidence of syphilitic aortitis. The circumference of the aortic ring was 8.0 cm., but, as a result of a remarkable, saccular, onion-shaped dilatation of the root of the aorta, the aortic circumference on the line of the commissural attachment was 12 cm. There was a difference of at least 4 cm. in the circumference of the aorta at this level and at the aortic ring.

DISCUSSION

We were unable to include this type of aortic regurgitation in the current classification of valvular disease. We wish to emphasize that these aortic valvular lesions may develop in any heart in which the aortic valvular ring has dilated; therefore, they are devoid of etiologic significance. We have noted them even in young and middle-aged patients with rheumatic heart disease, but always in the presence of a dilated aortic ring. This report is concerned primarily with the usually elderly hypertensive persons whose aortic regurgitation remains etiologically a matter of doubt, and who constitute a group which is entirely different from that of typical aortic insufficiency of infectious origin. The possible importance of arteriosclerotic degeneration as an etiologic factor in such cases must be considered. Osler, who described "arteriosclerotic" regurgitation,[2] thought that the lesion was similar to that of chronic endocarditis. Today we know that the aortic valvular lesion caused by arteriosclerotic degeneration is characterized by (1) calcareous infiltration beginning at the bases, and later involving the bodies, of the leaflets, the corpora arantii, and the sinuses, and (2) by the yellow, opaque, subintimal infiltration of atheroma. The lesions of

"mechanical" regurgitation are clearly different. We also know that arteriosclerosis of the aortic valve leaflets causes stenosis rather than regurgitation. It is likely, however, that some of Osler's cases were identical with those herein described, for he mentioned, under the heading "relative insufficiency," the infrequent occurrence of aortic regurgitation associated with dilatation of the aortic ring and adjacent arch.

The valvular lesions in most of our cases were prominent enough to engage the attention of the pathologist. In some cases not included in this series, the lesions were slightly developed, and consequently dismissed as being insignificant. Clinical observations, however, revealed the presence of aortic valvular insufficiency. On the other hand, we have not infrequently noted this type of valvular sclerosis in the absence of any clinical record of aortic regurgitation. The pulse pressure in such cases was invariably increased, and one may suspect that short diastolic aortic murmurs, with little or no transmission, may have been missed by the examiner.

Since dilatation of the aortic ring or supravalvular dilatation appeared to be the cause of this type of aortic insufficiency, it is likely that the valvular lesions were the result, rather than the cause, of the insufficiency. The normal aortic leaflets were unable to meet the demand for increased coverage, and, despite compensatory elongation (often seen), they were unable to prevent a leak. The regurgitation in the beginning was probably very slight, gradually eroding the corpora arantii and eventually giving rise to the lesions herein noted. These lesions may thus be regarded as an example of structural change secondary to functional insufficiency. The recognition of these lesions is not unimportant, in our estimation, for they appear to be characteristic. They lend credence to the opinion once held by some clinicians that functional aortic valvular insufficiency is an entity, and that it can exist despite the presence of diastolic hypertension.[4] The absence of objective evidence made the question hypothetical. Dilatation of the aortic ring was not regarded as satisfactory evidence, for terminal relaxation of heart chambers and their valvular rings is a common occurrence. The time factor is of some importance, which may be the explanation of reports of aortic insufficiency which was termed "functional" because there was no pathologic valvular change. It is our impression that few patients with aortic insufficiency show a complete absence of valvular deformity.

The differential diagnosis in elderly persons is concerned chiefly with the possibility of syphilitic infection. We have previously pointed out that positive serologic reactions may be anticipated in at least 95 per cent of all patients with truly syphilitic aortic regurgitation, excluding those who have recently had specific treatment.[13] This is in contradistinction to the 65 per cent or 70 per cent of positive reactions in uncomplicated aortitis. This conclusion was reached after study of necropsy material in which we segregated the occasional cases of "mechanical"

regurgitation and of healed dissecting aneurysm with aortic regurgitation which not infrequently are regarded as syphilitic because of the deceptive gross appearance.[13] The serologic reactions are thus of great importance in the analysis of these cases. We now believe that aortic regurgitation in untreated patients more than 50 years of age should not be considered syphilitic if the blood Wassermann and Kahn reactions are repeatedly negative. This single criterion appears to be reliable regardless of the patient's race or occupation, or any other factor that may ordinarily influence the diagnosis. The presence of auricular fibrillation in a case of aortic regurgitation in which the serologic reactions are negative almost certainly indicates that the lesion is not syphilitic. When "mechanical" regurgitation is accompanied by positive serologic reactions (a minority in our group), the diagnosis will remain, in most instances, an enigma until the day of necropsy. However, the presence of a loud, snapping aortic second sound, in addition to the diastolic aortic murmur, is suggestive of dilatation of the aortic ring, as pointed out by Scott.[14]

SUMMARY

Some persons, mostly men beyond middle age, exhibit signs of aortic regurgitation which is not caused by syphilis, rheumatic heart disease, bacterial endocarditis, or arteriosclerotic degeneration. Hypertensive cardiovascular disease is usually present.

This type of aortic regurgitation may be unaccompanied by most of the peripheral phenomena which are characteristic of aortic insufficiency of infectious origin. The diastolic murmur is usually merged with an accentuated aortic second sound. Patients with this lesion eventually die of congestive heart failure. Precordial pain is infrequent. Auricular fibrillation is common.

Dilatation of the aortic ring is present in most cases. Occasionally, only supravalvular dilatation of the aortic arch occurs. In all cases the aortic leaflets appear insufficient to meet the need of increased coverage. They often show compensatory elongation. Depending on the length of the survival period, there is a variable development of structural changes in the aortic leaflets; this is apparently secondary to the dilatation of the aortic ring and is brought about by the eroding action of slow leakage. The change consists of a sclerotic thickening of the mid-portion of the free margin of the leaflet, without involvement of the commissures. The latter, however, may be slowly pulled apart in the course of marked ring dilatation. Bicornate lesions and sclerotic lipping in the mid-portion of the free margins of the leaflets are characteristic of this type of regurgitation.

Syphilis may coexist in some cases; it may cause aortitis without involving the aortic valvular structure. Occasionally there may be both ring dilatation ("mechanical" insufficiency) and true syphilitic aortic valvular disease.

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THE ROUTINE USE OF CEDILANID IN CLINICAL PRACTICE

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EVER since Withering first broke down the herb medicine of the village witch and discovered that it was the foxglove which acted upon "the dropsy," research workers all over the world have been attempting to break up digitalis into its active ingredients. One glycoside after another, each supposedly free of toxic effects, has been isolated and recommended as the active principle of digitalis. These claims, however, have never been substantiated clinically, and the perfect cardiac drug has remained the will o' the wisp of the cardiologist. Therefore, when Stoll[1] isolated a glycoside from *Digitalis lanata* which differed from any of those in the *Digitalis purpurea* group, a new incentive was given to this search for the drug of choice in heart failure. This new glycoside has been called Lanatoside C, or Cedilanid.

To begin with, it is important to realize that the use of digitalis in the form of the whole leaf has marked disadvantages. The most important of these, from the clinician's point of view, is that there has never been a completely satisfactory method of assaying the preparation so that any tablet of digitalis leaf will always produce the same result in any given case. Gold and his co-workers[2] proved this point by some excellent research which most clinicians had known about for many years. Their carefully controlled experiments showed that, although the cat method of bio-assay was more nearly parallel to the efficacy of the drug in man, the frog method, on the other hand, bore almost no relation to the action of the drug on the human heart. Moreover, the cat method cannot be entirely relied upon, because patients take digitalis by mouth, and its glycosides are absorbed differently from various gastrointestinal tracts, whereas, in the cat method of assay, the drug is given intravenously, and absorption plays no role.

For a long time we, like many others, have felt the need for a preparation the action of which in any given case would be known at all times, so that no matter where the patient bought his digitalis, we could expect a specific action from a given amount of the substance. In our cases we had used practically all of the previously isolated glycosides without much success. In reviewing the literature, we came upon the work done on Cedilanid and immediately became interested in its use.

Experimentally it has been shown that this glycoside has a greater margin of safety than all the other *Digitalis lanata* glycosides, and, at the same time, brings about greater cardiac efficiency.[3] It has also

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been shown in animals that Lanatoside C will not produce a significant reduction in coronary blood flow, as measured by the thermostromuhr.[4] After this experimental work on animals, Fahr and LaDue[5] began to use the drug on a large group of patients in the Minneapolis General Hospital. When auricular fibrillation was present, its action was quite rapid and effective. They observed that in the treatment of congestive heart failure its action was excellent, even in the presence of normal sinus rhythm. They also met with good results in auricular paroxysmal tachycardia and auricular flutter, and they came to the conclusion that this preparation is less toxic in many instances than *Digitalis purpurea*. They found that the substance is stable, and, in therapeutic doses, does not damage the heart muscle of the dog even when administered daily for a period of three months.

Sokolow and Chamberlain[6] gave Cedilanid intravenously and found that its rapidity of action was its most striking clinical feature. They continued their studies, using both the oral and intravenous preparations, and concluded that the rapid absorption, constant potency, and rapid action of Cedilanid gave it definite advantages over *Digitalis purpurea*.[7]

We selected a mixed group of hospital outpatients, hospital ward patients, and private ambulatory and bedridden patients. Seventy-five per cent of these had been receiving digitalis for varying periods of time, and we were well aware of the difficulties involved in controlling their maintenance dosage; the remaining 25 per cent had never taken digitalis. The average total oral dose for digitalization was 15 to 20 tablets of Cedilanid (7.5 to 10 mg.). When the rapid and massive method of digitalization was used, the total dose of Cedilanid was approximately 10 to 15 tablets (5 to 7.5 mg.). The average maintenance dose was 1 to 3 tablets daily (0.5 to 1.5 mg.). Ninety-eight per cent of the group responded to the oral administration of Cedilanid most admirably. The usual criteria for improvement were used, namely, disappearance of edema in the lower extremities, of ascites, and of enlargement of the liver, reduction in pulse rate, lowering of venous pressure, and electrocardiographic evidence. Almost uniformly the action began sooner than that of digitalis leaf preparations, and the drug was also eliminated more rapidly. Most important of all was the fact that, once a maintenance dose was established, this could be continued indefinitely, providing the patient had no sudden change in his condition brought about by overexertion or coronary failure.

Two of the one hundred patients thus studied, of whom one had received digitalis and the other had not, both of whom had chronic auricular fibrillation, could not be controlled by the oral administration of Cedilanid, even when the dose was increased to 0.5 mg. six times a day. Both patients responded well to whole leaf digitalis. We have no way of explaining this peculiar fact, except that in certain

cases more than one glycoside may be necessary, or that some glycoside other than Lanatoside C may be the only one capable of acting under certain conditions. Only carefully controlled animal experiments can settle this question.

Judging from our experience with Cedilanid, it has a definite place in the armamentarium of the cardiologist. It is true that in large enough doses it will give the same toxic effects as *Digitalis purpurea;* nevertheless, the margin of safety is greater, and the rapid elimination of the drug diminishes the duration of the toxic symptoms. Finally, let us reiterate that once the dosage has been established, one need not worry about the possibility that each new prescription may be stronger or weaker, for we are dealing with a crystalline substance which is standardized by weight, and is therefore not subject to the variations of bio-assay.

SUMMARY

1. The pharmacology and chemistry of Cedilanid (Lanatoside C) are reviewed briefly.

2. The oral preparation was found to be constant in its action in clinical practice.

3. It was effective in ninety-eight of one hundred cases in which it was tried. No apparent cause for its failure could be found.

4. In those cases in which Cedilanid was effective, its toxic action was similar to that of *Digitalis purpurea,* but passed off more quickly.

5. Cedilanid is an efficient glycoside of *Digitalis lanata,* and has a definite place in cardiac therapy.

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THE ELECTRICAL CONDUCTIVITY OF THE TISSUES NEAR THE HEART AND ITS BEARING ON THE DISTRIBUTION OF THE CARDIAC ACTION CURRENTS

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IN THEORETICAL studies of the factors which determine the form of the electrocardiogram, it has usually been assumed that the heart is, in effect, immersed in an extensive medium which may be regarded as homogeneous with respect to those properties which determine the distribution of electrical currents of the kind produced by the heartbeat.[1-3] Those who have made this assumption have not maintained that it is strictly in accord with the facts, but merely that, considering the purposes which they had in mind, it represents the true situation with adequate accuracy. Recently the validity of this claim has been challenged as a result of the interpretation placed upon indirect experiments of various kinds.[4-7] So far as the writers have been able to ascertain, however, systematic direct measurements of the specific electrical resistances of the living tissues of anesthetized mammals have not previously been made. This is because of the great technical difficulties encountered in the application to such tissues of the methods available to the physical chemist for the measurement of specific conductivity.[8-12] It is the purpose of this article to describe the development, properties, and use of simple electrode systems which we have employed to measure the specific resistances of living tissues in situ.

Theoretical Considerations.—The current flow through an electrolyte or other conductor in an ordinary conductivity cell is determined by the size and shape of (a) the electrodes and (b) the walls of the cell. In the simplest case of plane circular electrodes, located at the ends of a cylindrical tube and perpendicular to its axis, the resistance, R, is defined by the equation

$$R = TL/A$$

where T is the specific resistance; L, the length of the tube; and A, its cross-sectional area. The cell constant is then $K = R/T = L/A$. For more complicated cell forms the cell constant is usually determined experimentally by the use of an electrolyte of known specific resistance, T. For the present purpose, however, it is not practical to obtain nonconducting boundaries corresponding to the walls of a cell from which the cell constant may be computed or measured. The obvious expedient is then to consider an unbounded or infinite medium.

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The resistance between two small spherical electrodes of radii a and b separated by a distance l in an infinite medium of specific resistance T is given by Mason and Weaver[13] as

$$R = T/4\pi \left(\frac{1}{a} + \frac{1}{b} - \frac{2}{l}\right) \qquad (1)$$

As l is made large its effect becomes negligible, and the resistance is the sum of two parts, one for each electrode. The cell constant for a single spherical electrode is then $\mu = 1/4\pi a$. Similarly, for a buried disc of radius a, $\mu = 1/8a$, and if the disc rests on a flat surface of the medium, $\mu = 1/4a$.

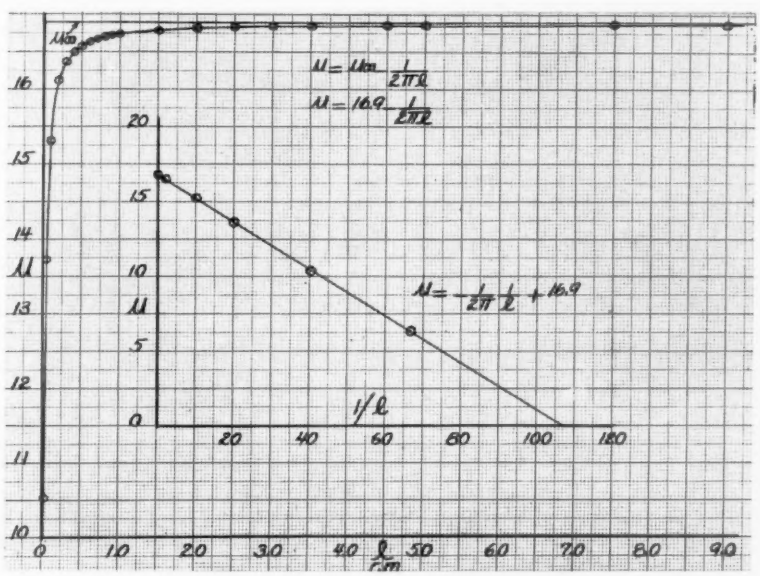

Fig. 1.—Curves showing the relation between the cell constant, $\mu = R/T$, of a pair of point electrodes placed in an infinite medium and the distance between them, l. The large graph represents the equation $\mu = \mu\infty - \frac{1}{2\pi l}$, which was obtained by substitution of values for a and b and α and β in Equation 2 (see text). The small insert shows that when μ is plotted against $1/l$, a straight line is obtained.

The most practical experimental technique has been to use cylindrical wires which were insulated except at the ends. The electrodes in contact with the electrolyte or tissue were then circular discs with the diameters of the wires. With thick insulation the cell constant of each electrode would be that of a disc applied to the surface, or $\mu = 1/4a$. The cell constant has not been calculated for thin insulation, but it will be smaller than $1/4a$, and will probably approach the value $1/8a$, which is that of the buried disc with both faces exposed. In general then, we may write

$$R = T\ (1/\alpha a + 1/\beta b - 1/2\pi l) \qquad (2)$$

where α and β depend upon the shapes of the electrodes and the insulation, but certainly lie between 4 and 4π. The relation between $\mu = R/T$ and l is shown in Fig. 1. If a and b are nearly equal and l is more than

twenty times the radius a, the proximity effect will be less than 5 per cent. The requirement of an infinite extent of a single tissue cannot be met rigorously, and the effects of adjacent tissue have been calculated. It has been found that if each electrode is more than twenty times its radius from the nearest surface, the boundary proximity effect is less than 5 per cent for any conductivity of adjacent tissue from zero to infinity.

If two electrodes are placed more than twenty times their radii from each other and from the boundaries, the cell constant should be within 10 per cent of the value for a large separation in an infinite medium. For any particular organ or tissue these conditions can always be met by making the electrodes sufficiently small, but other difficulties may arise. The electrodes should not be as small as the tissue cells, for the measured resistance will then depend upon their position relative to the nearest cells. Furthermore, as the electrodes are made smaller, the polarization impedance of the electrode surface increases more rapidly than the measured resistance. A limit is then set by the efficacy of the platinization which can be obtained. In the case of a disc, the platinization near the center is not fully effective because the current density is much lower there than it is near the edge.

Equipment.—A portion of the work reported here was performed in the Electrochemical Laboratory and the remainder in the Heart Station. As regards essentials, the equipment was the same in both places. It consisted of a modified Jones and Josephs[8] bridge, which measured parallel resistance (R_p) and capacity (C_p), a thermostat, a standard conductivity cell of a design recommended by Jones and Bollinger,[10] an oscillator, and platinum electrodes of various types. The bridge used in the Heart Station differed from that employed in the Electrochemical Laboratory in that it had an amplifier in the phone circuit. The oscillator used in the latter place had a fixed frequency of 1,000 cycles per second and a fixed output, whereas both the frequency and the output of the oscillator used in the former could be varied. The small electrodes hereinafter designated as point electrodes, or points, were made of platinum wire about 0.25 mm. in diameter and were insulated except at the tips by a variable thickness of glass.

EXPERIMENTAL RESULTS

Measurements of Point-Electrodes Systems.—Measurements were made with point electrodes in different combinations, at various separations, and in several media and shapes and sizes of vessels. Only those pertinent to the present investigation will be discussed. Aqueous solutions of sodium chloride, potassium chloride, ammonium chloride, hydrogen chloride, and zinc sulfate were used. For certain experiments the electrolyte was dissolved in 2 per cent agar-agar (Difco Bacto-Agar), which was subsequently allowed to solidify. The resistance of all aqueous solutions was measured in the standard conductivity cell be-

fore and after it was measured with the special electrode systems. A 3-liter beaker filled with the solution to be studied served as a first approximation to an infinite medium.

Electrode Polarization and Platinization.—The polarization impedance at the surface of bare platinum was too large to permit the use of small electrodes of this material; consequently, all electrodes were electrolytically coated with platinum black before they were used. The point electrodes were platinized by passing current from a storage battery through them after they had been immersed in chloroplatinic acid. A commutator was used to reverse the polarity of the current once per second. The resistance in the external circuit, which was located mainly at the electrode-acid junction, varied continuously in an unknown fashion as the degree of platinization increased. As the elec-

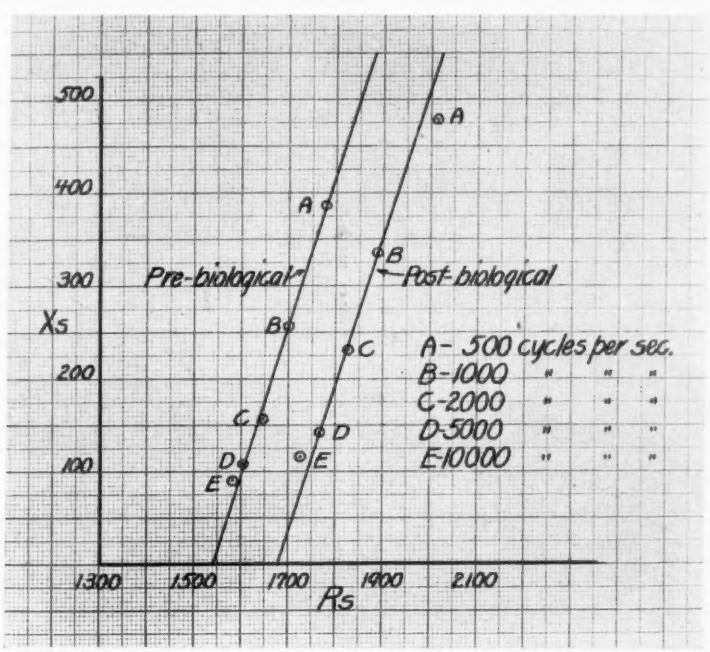

Fig. 2.—Impedance loci of a pair of point electrodes before and after they were used to measure the resistance and reactance of living tissue.

trodes were platinized for increasing lengths of time, the effects of polarization at first decreased rapidly and then more slowly (Jones and Bollinger[12]). After 150 seconds of platinization, the electrodes were usually satisfactory. The series resistance and reactance of such a pair of electrodes in normal saline were computed from the measured parallel resistance and capacity, and are plotted as an impedance locus in Fig. 2. The intercept on the resistance axis is the electrolyte resistance approached at high frequencies. The reactance and added

resistance at each frequency constitute the electrode polarization impedance. For many purposes this is negligible. It was found, however, that for measurements made at the single frequency of 1,000 cycles, the apparent cell constant of point electrodes increased as either the concentration or the temperature of the electrolyte was increased. For unselected electrodes the changes in the value of μ produced by variations in the temperature and concentration of the solutions studied amounted to between ±4.5 and ±8.5 per cent of its mean value. For any given concentration, μ was constant for a given pair of electrodes (separated by a distance of at least 3 cm.) to within 0.5 per cent. This constant did not vary with changes in the output of the oscillator at any frequency. These effects are probably results of the changes of the polarization impedance with concentration and temperature.

When two point electrodes were immersed in a 3-liter "infinite" medium, the point-point resistance and μ increased gradually with greater separation of the electrodes, but this increase was most rapid when the separation was less than 1 cm. From the data of Table I it was found that $\mu\infty = \frac{1}{a\alpha} + \frac{1}{\beta b} = 16.9\ cm.^{-1}$ If $a = b = 0.125$ mm. then $\alpha = \beta = +9.5$. This lies between the values of 8 for the double-sided disc, and 4π for the sphere, indicating that the surface was probably convex outward. Substituting this value in equation (2), the theoretical curve of Fig. 1 was obtained. It agrees well with the observations, and shows a proximity effect of 5 per cent for a distance of 2 mm.

TABLE I

COMPARISON OF THE OBSERVED VALUES OF μ AND THOSE CALCULATED FROM THE EQUATION, $\mu = \mu\infty - \frac{1}{2\pi l}$, OF FIG. 1

	μ	
l CM.	CALCULATED	OBSERVED
0.5	16.58	16.65
1.0	16.74	16.74
		16.81
4.0	16.86	16.81
4.5	16.86	16.86
5.0	16.87	16.88
10.0	16.90	

When the volume of the medium was reduced from 3,000 to 60 c.c. and the diameter of its cross section from about 15 cm. to 4.5 cm., the resistance and the relation between the resistance and the distance between the electrodes were the same (within the physical limitations as regards separation of the electrodes imposed by the smaller volume of the medium) as when the medium was more extensive. The data given in Table II indicate that the electrode proximity effect and the boundary proximity effect are about 1 per cent for the range investigated.

TABLE II

VALUES OF THE CELL CONSTANT, μ, OF A PAIR OF POINT ELECTRODES IN A RESTRICTED MEDIUM (60 C.C. OF NH_4Cl SOLUTION IN A CYLINDER 4.5 CM. LONG, AND 4.5 CM. IN DIAMETER) AND IN A MORE EXTENSIVE MEDIUM (3,000 C.C. OF NH_4Cl SOLUTION IN A LARGE BEAKER)

	DISTANCE BETWEEN ELECTRODES, l CM.	μ
Restricted medium	1.5	18.69
Restricted medium	2.0	18.77
Restricted medium	2.5	18.84
Unrestricted medium	1.5	18.90

When 2 per cent by weight of agar-agar was dissolved in aqueous solutions of a number of inorganic substances and permitted to solidify, it caused no change in the conductivity of the original aqueous solutions. The resistance-distance relationship of the point-point electrode system inserted into the agar block was the same as for a medium of the original composition and of comparable shape and volume.

As a test of our method, we calculated from point electrode measurements the resistance that would be observed when the medium was placed in a standard conductivity cell, and then attempted to confirm our prediction by observation. Since $R_k/R\mu = K/\mu$, the factor K/μ may be ascertained by measuring the resistance at a given frequency of a solution of known conductivity by both methods. When $R\mu$ has been measured with an unknown solution, R_k may be calculated. As a check, R_k for the unknown solution may be measured directly. For example, the resistance (R_k) of an aqueous solution of approximately 0.9 per cent NaCl measured 2,574 ohms in the standard conductivity cell. The predicted value of R_k for an agar block containing 2 per cent agar-agar dissolved in 0.9 per cent NaCl, obtained by computation from $R\mu$, was 2,584 ohms.

Summary on Electrode Systems.—The properties of simple point-electrode systems were investigated theoretically and experimentally with reference to their suitability for the measurement of specific conductivities under a variety of conditions. In the form used by us these special electrode systems have certain limitations and do not permit measurement of specific conductivity with the same degree of precision as the standard conductivity cell. They do, however, make it possible to ascertain, with an accuracy sufficient for many purposes, the specific conductivity of materials which cannot be placed in a standard conductivity cell and have not heretofore been satisfactorily measured.

MEASUREMENT OF THE SPECIFIC RESISTIVITY OF LIVING MAMMALIAN TISSUES

Our animal experiments were carried out upon dogs which were anesthetized with morphine and urethane. Various operative procedures were used to gain access to the organs or tissues studied. When the chest was opened, the lungs were ventilated with room air by

TABLE III

MEASUREMENTS OF THE SPECIFIC RESISTANCE OF LIVING TISSUE IN OHM CM.

DATE 1938	MUSCLE	LIVER	LUNG	HEART	PERICARDIUM	FAT	BLOOD	SERUM
4/28	492-506 425-416	524-460 513	768-791 810-757 784-839 713 *401 624	153-143 307-285	434-405			
5/9	707-565	1,083-789	850-719	212-199				
5/12	722-525 752 701-569	517-419	†1,368-1,332					
5/17	552-539 587-527	778-758	†1,563-1,243	265-251 224-212		1,960-1,757		
5/19	636-672		765-681					
5/20	1,103-938					2,450-1,859		
6/1	426		897-804 686-615					
6/4	1,532-760	697-390	†1,278-1,108	185-151				
6/6	610-320	595-222	†1,257					
6/7								178-98
6/9							235-195 225-175	

The figures given first are those based on the prebiologic calibration of the point electrodes.
The figures given last are those based on the postbiologic calibration of the point electrodes.
*Lungs deflated.
†Lungs superinflated.

means of a pump designed by Erlanger and Gesell.[14] All measurements of tissue conductivity were preceded by the calibration of a set of two point electrodes separated by a distance of 2 or more centimeters. The calibration consisted of measuring, at frequencies of 500, 1,000, 2,000, 5,000, and 10,000 cycles per second, the parallel resistance and parallel capacities required to balance the bridge after the electrodes were immersed in an "infinite" medium of approximately 0.9 per cent saline at a temperature close to that of the tissues to be studied. The conductivity of the 0.9 per cent saline, maintained at the same temperature, was measured independently in a standard conductivity cell. As soon as the point electrodes had been standardized, they were placed on the surface or within the substance of the tissue or organ under investigation, and the parallel resistance, R_p, and parallel capacitance, C_p, required to balance the bridge for the above frequencies were ascertained as rapidly as possible. After the tissue measurements were completed, the electrodes were restandardized.

TABLE IV

AVERAGE VALUES FOR THE SPECIFIC RESISTANCES OF LIVING TISSUES IN OHM CM.

TISSUE	NO. OF ANIMALS	NO. OF OBSERVATIONS	SPECIFIC RESISTANCE PREBIOL. CALIBRATION	SPECIFIC RESISTANCE POSTBIOL. CALIBRATION
Muscle	9	13	711	
(somatic)	9	11		575
Liver	6	7	672	
	6	6		506
Heart	4	6	224	207
Pericardium	1	1	434	405
Lung				
At end of normal inspiration	4	9	766	
		7		744
Superinflated	4	4	1,367	
	3	3		1,227
Deflated	1	1	401	
Fat	2	2	2,205	1,808
Serum		1	178	98
Blood		2	230	185

The specific resistance of the saline solution (approximately 0.9 per cent) used in standardizing the point electrodes was roughly 50 ohm cm. at 37° F., or about one-fourth that of defibrinated blood.

The series resistance and reactance at each frequency were calculated for the electrodes in saline before and after the tissue measurement.* The characteristics in each case are shown in the impedance loci of Fig. 2. The "cell" constant and the electrode polarization were not the same after the electrodes had been in contact with tissue as

*In computing the series resistance, R_s, and series reactance, X_s, the following formulas were employed (see Cole and Cole[15f]):

$$R_s = \frac{R_p}{(1 + R_p^2 C_p^2 W^2)} \qquad X_s = \frac{R_p^2 C_p W}{(1 + R_p^2 C_p^2 W^2)}$$

R_s = Series resistance; X_s = series reactance; R_p = parallel resistance; C_p = parallel capacitance; $W = 2\pi$ frequency.

before, perhaps because of the absorption of proteins. The specific resistance of the tissue and the polarization corrections were calculated from these data. Higher values for the specific resistivity of the tissue were usually obtained when the first or prebiologic calibration curve was used than when the second or postbiologic calibration curve was used, but the reverse was sometimes the case (Tables III and IV). It should be pointed out in this connection that since several tissues were measured with the same pair of electrodes in the course of each experiment, the prebiologic calibration for all except the first tissue studied was also the postbiologic calibration for the preceding observation. In some instances the series resistance and reactance of the tissue were calculated, and the polarization resistance and reactance subtracted at each frequency.

The impedance loci for muscle, liver, and lung shown in Figs. 3, 4, and 5 were obtained by plotting the resistances and reactances which had been computed in this manner. These loci are probably circular arcs such as have been found over wider frequency ranges for other tissues and cells.[15d, 15f] It is possible to extrapolate the lower frequencies and direct current resistances from these data. However, the resistance for the range of frequencies below 500 cycles per second, which occur in the electrocardiogram, are only slightly larger than those at 1,000 cycles. Consequently, only these latter values will be considered.*

The simplest biologic tissue studied was defibrinated dog's blood, which consisted, by volume, of half cells and half extracellular fluid. About 500 c.c. of defibrinated blood in a beaker with a diameter of 10 cm. constituted the "infinite" medium. The electrical resistance was measured both in the standard conductivity cell and by calibrated point-electrode systems. The resistance and capacitance measured by the point electrodes in a large medium are resident in a relatively small volume of circumelectrodal medium, and are not influenced to any great extent by the medium lying outside this region. This is shown by measurements made by immersing the point electrodes in defibrinated blood before and after the blood was allowed to sediment. The resistance of the mixed whole blood was 4,900 ohms; whereas, after sedi-

*The specific resistances shown in Table III were computed in the following way. Approximately 0.9 per cent saline solution at body temperature was measured in a standard conductivity cell at the beginning and again at the end of the experiment, and the mean of the two readings (R_k) was used. The cell constant of the conductivility cell, K, was known to be 39.37. The same solution was measured with the point electrodes before and after each observation. The prebiologic constant of the point electrodes was ascertained from the first reading, $R\mu$ (at 1,000 cycles per second), by the formula:

$$\mu = K \frac{R\mu}{Rk}$$

The postbiologic value for the cell constant (μ) of the point electrodes was ascertained from the second reading in the same way. The specific resistance of the tissue was computed by dividing the measured resistance of the tissue at 1,000 cycles per second by the cell constant.

mentation was complete and the electrodes were in the serum, a reading of 2,940 ohms was obtained. The latter value was evidently due largely to the resistance of the serum.

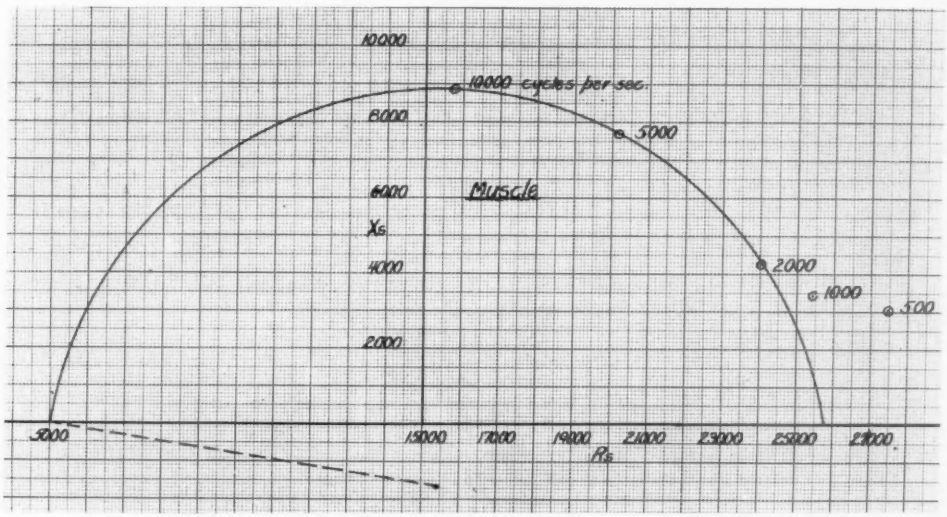

Fig. 3.—Impedance locus of triceps muscle based on experiment of May 19, 1938.

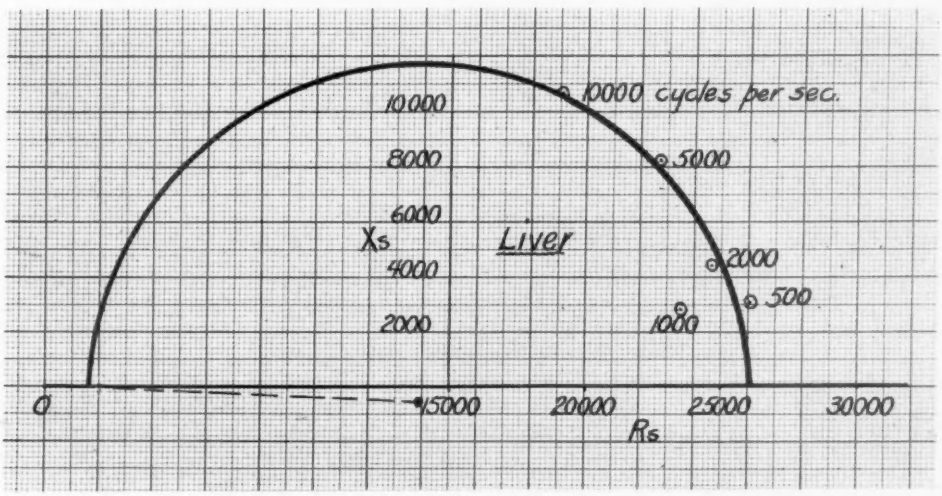

Fig. 4.—Impedance locus of liver based on experiment of May 9, 1938.

Lungs.—In a number of experiments in which the pulmonary specific resistivity was measured, the lungs were rhythmically inflated in a manner which approximated normal ventilation before the chest was opened. Many sites on the lung surface from the hilar to more lateral regions and from apical to basal fields were explored. When the electrodes were inserted into the lung tissue, the resistances obtained were

entirely comparable to those obtained with the electrodes on its surface. Since the resistance of lung tissue varied from expiration to inspiration, the specific resistance was measured arbitrarily in most animals under conditions approximating the height of normal inspiration. The range of variation from normal expiration to normal inspiration was ascertained by holding the lung in an expiratory, and again in the maximal normal inspiratory, position until measurements could be made. When a series of measurements, over the range of frequencies used, was made with the electrodes in a given position on either the surface or in the depths of the tissue, and was then repeated immediately, there was practically no difference between the second and the initial series of measurements. This indicates that possible tissue changes due to placing of the electrodes did not have an important effect upon the final value for the resistance under these experimental

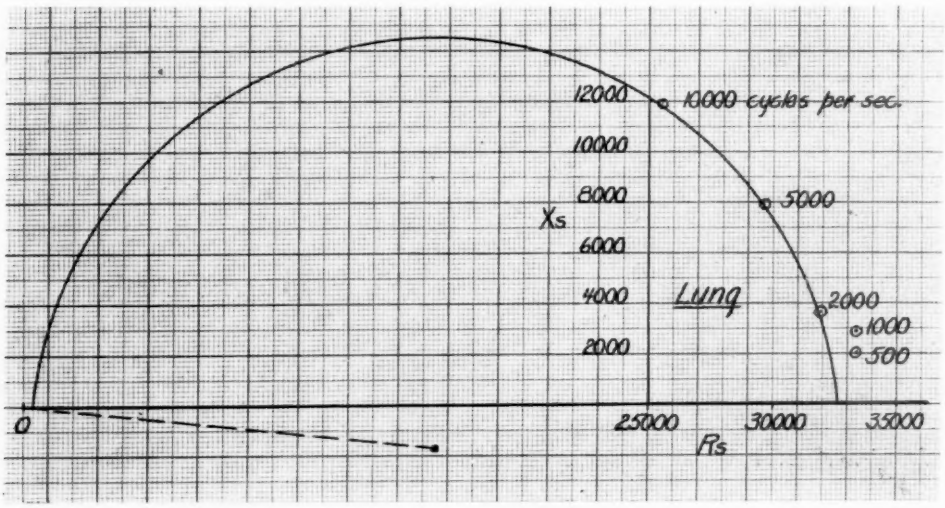

Fig. 5.—Impedance locus of lung based on experiment of May 9, 1938.

conditions. In a number of instances the lungs were overinflated until they were grayish-white in color, and bulged from the chest so that both expiratory and inspiratory volumes were greatly in excess of those possible in the living animal with an intact thoracic cage. The maximal resistance of the lung tissue of living animals under these conditions was about twice as great as that at the height of normal inspiration. When, however, death occurred suddenly with the lung at any volume, as a result of ventricular fibrillation induced by multiple air embolism of the smaller branches of the coronary arteries, the resistance of the rhythmically inflated lungs rose beyond the range of the measuring instruments.

Muscles.—The specific resistance of voluntary muscles (triceps, quadriceps, biceps, deep muscles of the back, intercostal muscles, recti, and diaphragm) was ordinarily studied after the fascial envelopes were incised. The measurements made on muscles included observations on the midportions, as well as on regions near the ends, where the connective tissue components became the more prominent constituents. The average resistance of muscle was not very different from that of normally inflated lung tissue. The specific resistance of the liver, as measured with the electrodes on the surface and in the depths of its substance, was nearly the same as that of muscle and lung tissue.

An attempt was made to measure the resistance of cardiac muscle during diastole. This was an especially difficult task when the heart was beating rapidly. The specific resistance of living cardiac muscle, with the electrodes either on the surface or imbedded, was found to be approximately one-third that of lung, muscle, and liver tissue, and about the same as that of blood. Fat and connective tissue had the highest resistances of any tissues measured. Bone and nerve were not studied.

The average values of the specific resistances of the various tissues are given in Table IV.

SUMMARY AND CONCLUSIONS

The specific resistances of living mammalian tissue in situ may be ascertained by measurement of the resistance between two small electrodes placed upon its surface or within its substance. The basis and scope of this method have been considered theoretically and verified by measurements of simple electrolytes and blood.

Measurements on the living tissues of the anesthetized dog show that muscle, normally inflated lung, and liver have specific resistances of the same order of magnitude. These measurements establish experimentally the validity of the assumption that the errors in theoretical studies of the form of the electrocardiogram, made by considering the tissues which surround the heart uniform with respect to their specific resistivity, are of no practical importance.

The writers wish to thank Dr. Frank N. Wilson for continued encouragement and valuable suggestions during the course of our work. We are grateful to Dr. A. L. Ferguson, of the Department of Chemistry, University of Michigan, who extended to us facilities in the Electrochemical Laboratory and helped us with some of our technical problems. We are particularly indebted to Dr. Kenneth S. Cole, of the Department of Physiology of the College of Physicians and Surgeons, Columbia University. It was he who suggested that point electrodes might be used for the measurement of tissue conductivities, and he was kind enough to provide the theoretical background of our problem. He also aided us on numerous occasions with advice and criticism. Without his assistance, this study could not have been possible.

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SHORT P-R INTERVAL WITH PROLONGED QRS COMPLEX: ALLERGIC MANIFESTATIONS AND UNUSUAL ELECTROCARDIOGRAPHIC ABNORMALITIES

Report of a Case

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THE following case in which the electrocardiogram showed a short P-R interval and a prolonged QRS complex in a healthy person who was subject to attacks of paroxysmal tachycardia is reported because there were unusual clinical and electrocardiographic features, several of which have not been reported previously.

REPORT OF CASE

A 24-year-old, well-developed, and somewhat obese man was admitted to the hospital with the chief complaint of attacks of rapid beating of the heart.

The family history was irrelevant except that one brother had hay fever caused by sensitivity to pollen and hair. The previous personal history was irrelevant except for morning sneezing.

The patient stated that he had been subject to attacks of rapid beating of the heart as long as he could remember, and that his mother told him he had had these seizures since birth. At the age of 10 years a physician told him not to engage in any strenuous sports. When he disregarded this advice and played a game such as baseball, a paroxysm was usually precipitated. Overexertion and fatigue increased the frequency of the attacks. In civil life, the seizures usually came on Saturday or Sunday, after a busy week, and averaged about one every three weeks. In the first four months that he was in the Army the paroxysms were more frequent, and were thought to have been precipitated by calisthenics or marching double time.

A typical attack began in the evening and was preceded by a period when the heart seemed to beat irregularly. The tachycardia started suddenly by the "heart jumping off its axis, giving a real hard knock, and then beating fast." During a paroxysm the patient felt dizzy, sweated profusely, and had a frontal headache. Seizures during the preceding eight months had been accompanied by pain in the chest, radiating to both shoulders. An attack necessitated the stopping of any activity and lying down. The paroxysm usually stopped as suddenly as it began, and left the patient weak and exhausted for a period of six to twelve hours. Attacks lasted from ten minutes to twelve hours. Occasionally there was a period of several hours before or after a seizure when the heart seemed to beat irregularly, but, between attacks, the patient felt perfectly well. Sometimes the patient was able to abort paroxysms by forced expiration with the glottis closed.

Physical examination revealed a well-developed and well-nourished young man who was seventy inches tall and weighed two hundred pounds. The cardiac examination was negative, as was the entire physical examination.

Laboratory examination, including roentgenographic and fluoroscopic examination of the heart, serologic reactions, blood cell count, and urinalysis, was negative.

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Allergic examination showed that the patient was sensitive to the following: chicken, mackerel, cane sugar, green pea, chocolate, barley, sweet corn, spinach, coffee, oyster, strawberry, horse serum, dust, goat epithelium, feathers, wool, fish glue, orris root, timothy, plantain, ragweed, ash, elm, *Aspergillus*, *Monilia*, trichophytin, and *Ascaris*. Passive transfer sites were tested with food allergens that produced moderate or greater reactions on skin testing, with the following results: cane sugar, green pea, and chocolate were markedly positive; mackerel and spinach were slightly positive.

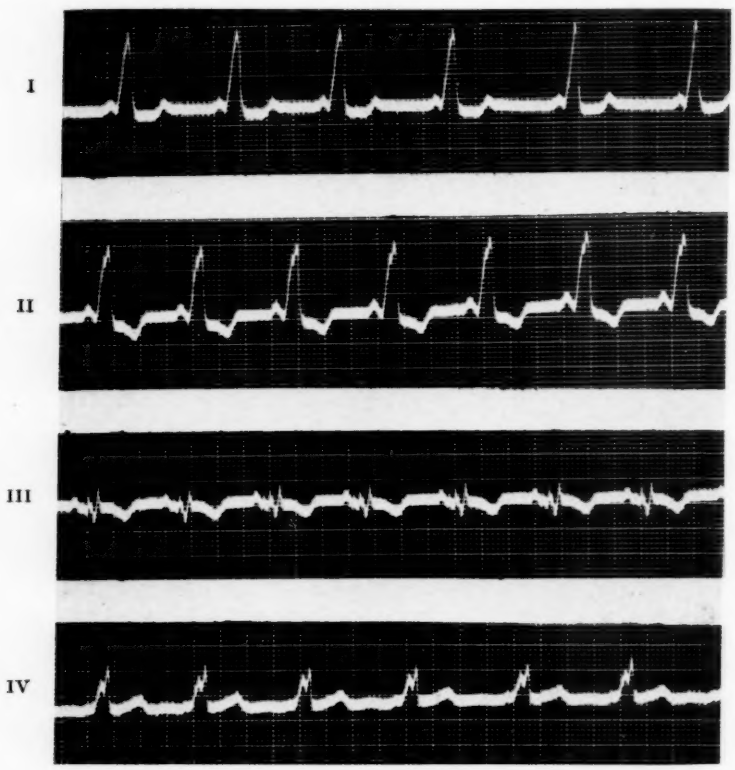

Fig. 1.

Electrocardiograms were obtained on this patient under many different conditions. These may be divided into several general groups, as follows:

The "normal" resting electrocardiogram (Fig. 1) showed a rate between 70 and 83, with slight sinus arrhythmia. The P-R interval was always 0.10 second. The QRS deflection was prolonged to 0.14 second, and the initial limb of this complex was slurred. The S-T segment was depressed in the limb leads, especially Lead II. The T wave was upright in Lead I and inverted in Leads II and III. The tracing was of the short P-R interval and prolonged QRS type which is associated with conduction through an accessory bundle, the bundle of Kent.

The tracing taken during an attack of tachycardia (Fig. 2) showed that the latter was supraventricular in origin, for the QRS deflection time was normal. The rate was about 180. The graph at the bottom of Fig. 2 is a strip of Lead II, taken during the attack while pressure was being applied to the carotid sinus. There are two normal complexes, the second of which has a P wave superimposed

on its S-T segment and is immediately followed by a ventricular complex which is transitional between the normal form and that present during the paroxysm. This process repeated itself several times, after which the tachycardia was resumed.

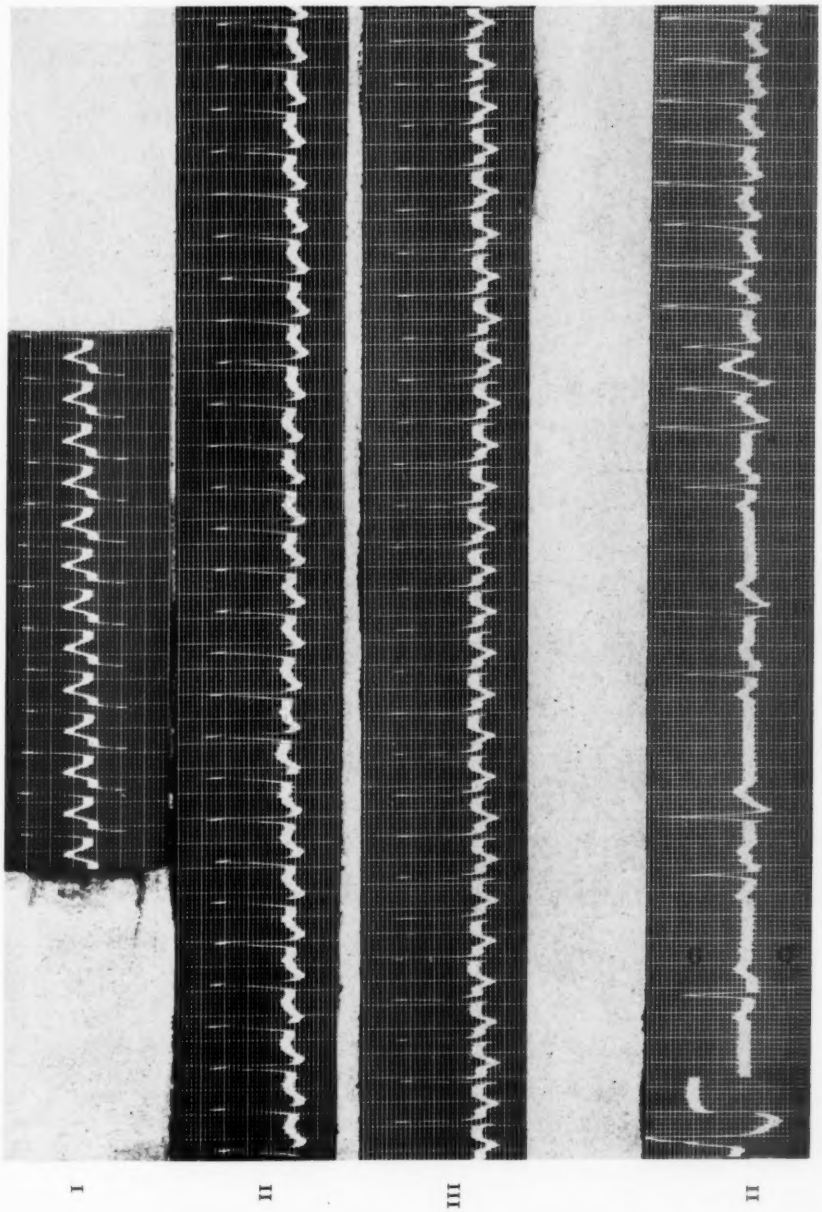

Fig. 2.

A tracing taken prior to his entry into this hospital (Fig. 3) showed a rate of 83 and an irregularity caused by premature beats. The prematurity was slight in Leads I and II, and more marked in Leads III and IV. In all leads except Lead III, there was a constant relationship between the complexes; that is, the normal

complexes were equally spaced, and so were the abnormal complexes. The normal complexes had a P-R interval of 0.18 second, a small Q_3, and an inverted T_3. The normal beats, therefore, were normal for a patient of his habitus (high diaphragm). The abnormal (premature) beats were similar to those in Fig. 1.

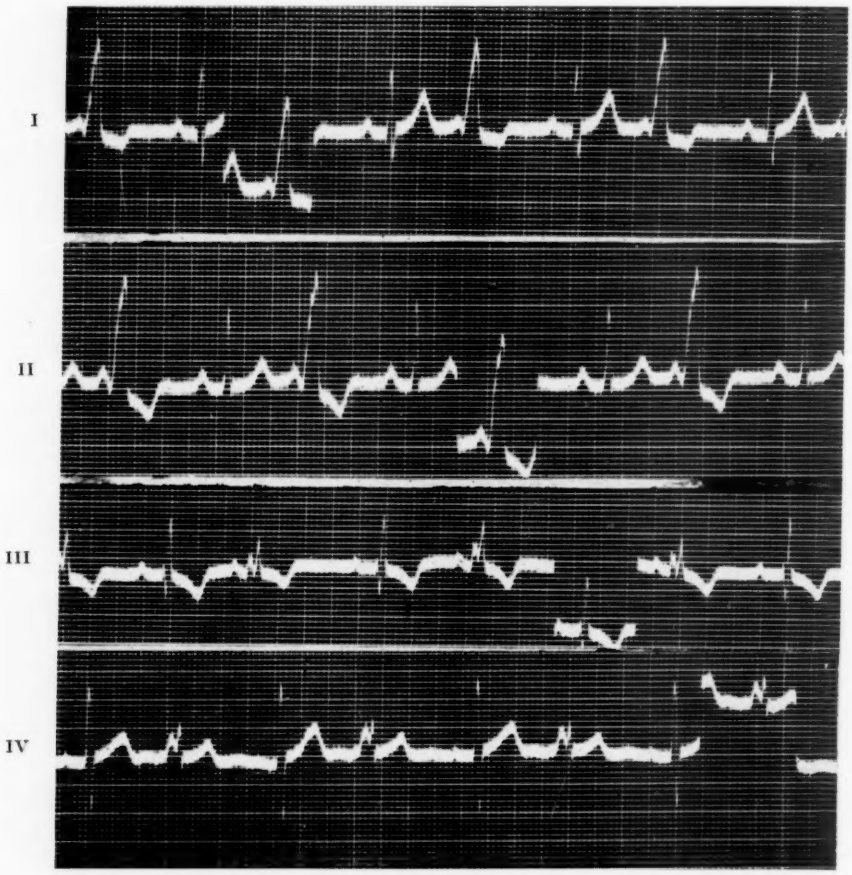

Fig. 3.

Long strips of Lead II were taken shortly before and after an attack (Fig. 4), during the period when the patient felt his heart beating irregularly. (*A*) The rate is 111. The heartbeat is regular, with normal and abnormal complexes alternating, except that the seventh abnormal complex is followed by two normal complexes. (*B*) The rate is 111. The heartbeat is regular, and two normal complexes alternate with an abnormal complex; all are equally spaced. (*C*) The rate is about 83. The heartbeat is irregular because normal and abnormal complexes alternate. The abnormal ventricular complexes are premature. Near the end of the strip, several abnormal complexes occur together. (*D*) The rate is 80 and the beating is irregular. Five normal complexes are followed by an irregular alternation of normal and abnormal complexes.

Strips of Lead II were taken on five occasions; the transition from "normal" rhythm to tachycardia is illustrated in the first four strips, and from tachycardia to "normal" rhythm in the last (Fig. 5). Fig. 5 *A-D* shows the result of carotid

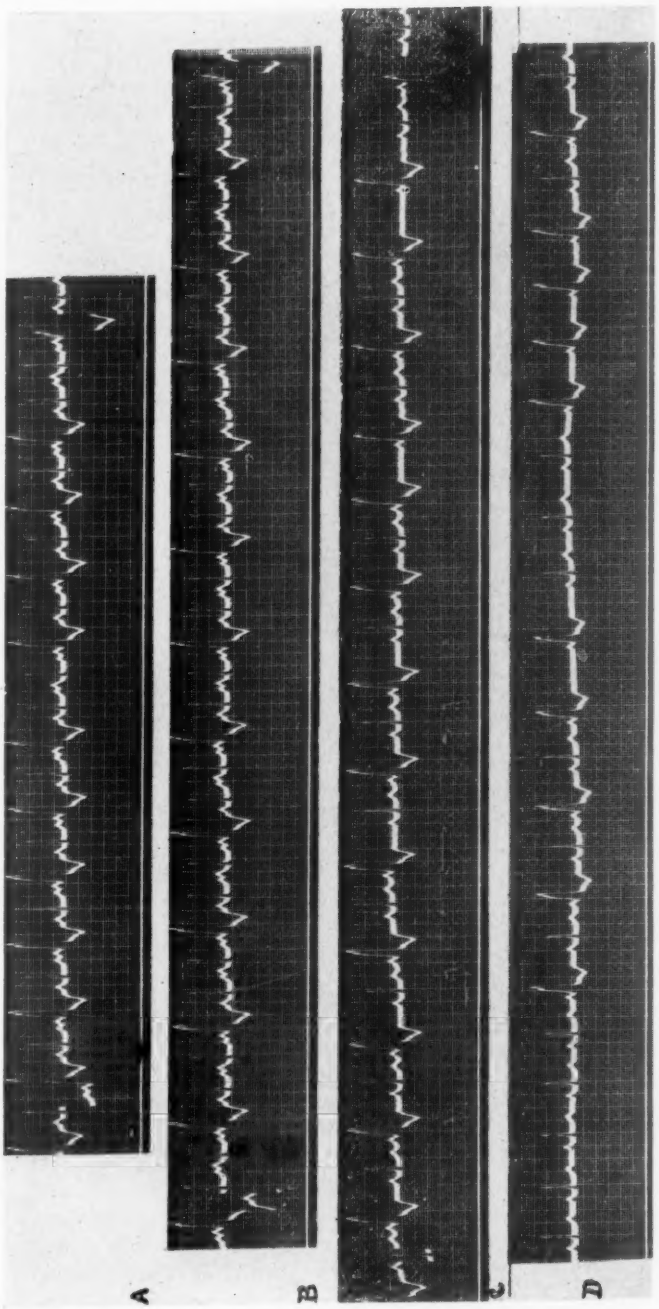

Fig. 4.—Strips of Lead II.

sinus pressure during an attack of tachycardia. Fig. 5 *A* shows what is probably the longest effect obtained by this procedure. In general, the effect of carotid sinus pressure lasted only a few beats before the tachycardia recurred. Fig. 5 *E* was taken just as an attack of tachycardia ended spontaneously.

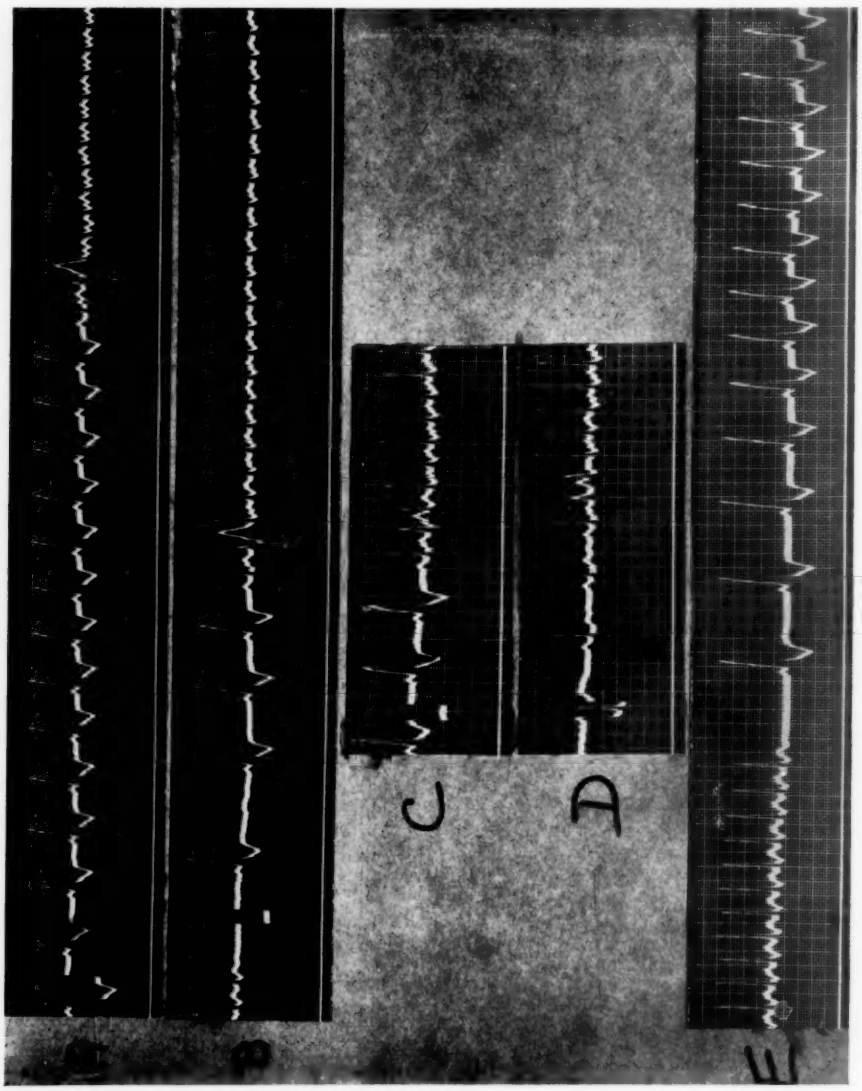

Fig. 5.—Strips of Lead II.

Tracings taken after exercise were essentially the same as in Fig. 1, except for an increase in rate. During ocular pressure (Fig. 6), the rate varied between 45 and 50 and there was a definite sinus arrhythmia. The tracing shows a lapse of 2.6 seconds between the first two complexes in Lead III. Note that the QRS complexes are of greater amplitude than those in Fig. 1; this increased amplitude makes the slurring less noticeable, but demonstrates that it involves only the initial component of the deflection. Tracings taken every five minutes after the administration of 1/50 grain of atropine sulfate were the same as that in Fig. 1, except

that the rate increased to about 90. With the increase in rate, the sinus arrhythmia became much less pronounced.

Progress.—Despite the physical rest provided by hospitalization, the patient continued to have attacks far more frequently than before; they occurred once, or sometimes twice, a week. Of the first four attacks, three occurred on Fridays, and the question was raised whether sensitivity to fish might be a precipitating factor. Consequently, fish was withheld on one Friday, but the patient had an attack on the same day after eating ice cream and drinking lemon soda. Several days later the patient was given fish for dinner but had no attack on that day.

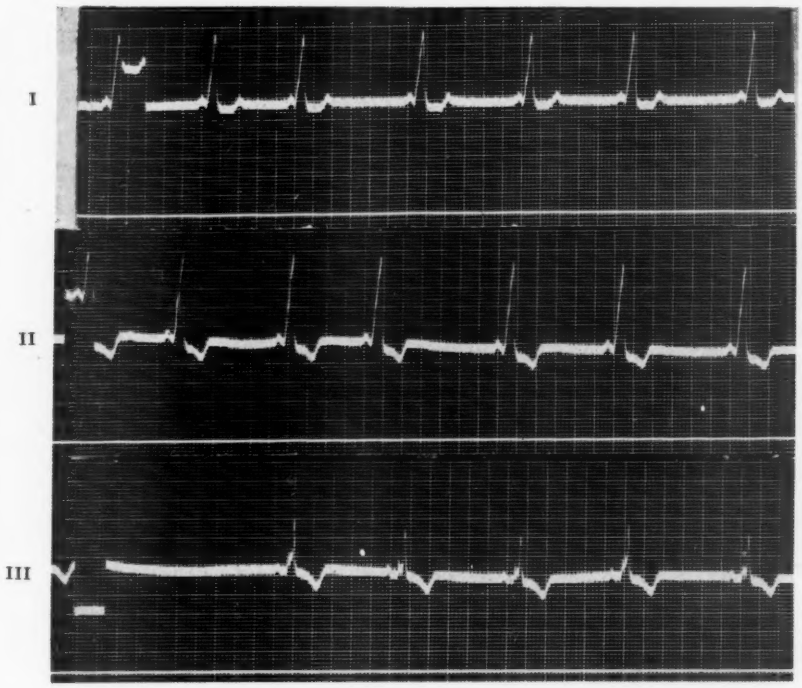

Fig. 6.

Subsequently, the patient was studied from the allergic standpoint. A list of substances to which he was sensitive has been given. He was then placed on a diet consisting only of lamb, rice, and milk for two days. On the third and fourth days, four teaspoonfuls of cane sugar were added twice daily. On the evening of the first day on which the sugar was given, the patient had an attack. The patient then was given nothing but lamb, rice, and milk for two more days. On the third day sugar was again added. This time, the patient noticed that his heart skipped irregularly on the first day the sugar was given, and that he had a definite attack on the second day. He was then placed on a full diet, except the foods to which he showed sensitivity. After several days on this diet, with no attacks, he left the ward, drank two bottles of a cola drink, and immediately had an attack. After explaining to the patient about the sugar content of soft drinks, he adhered rigidly to his diet and was more comfortable than at any time prior to his entrance into the hospital. He stated that he had never drunk soft drinks prior to hospitalization because he greatly preferred beer.

SUMMARY OF LITERATURE

Kent,[1] in 1914, published his observations, first made in 1892, on an accessory cardiac conduction bundle which crosses the auriculoventricular groove in the right lateral wall of the heart.

In 1915, Wilson[2] reported a case of mitral stenosis in which, during the course of a long period of observation, there were four different cardiac rhythms. When first observed (Wilson does not state whether the patient was febrile, nor does he give the pulse rate), the rhythm was normal. With slowing of the heart rate subsequent to deep breathing, a type of "bundle branch block" was found, together with a short P-R interval. Vagus pressure also caused this "block." Normal rhythm could be brought back by acceleration of the rate caused by $\frac{1}{50}$ grain of atropine or a succession of deep breaths. The patient had two attacks of paroxysmal tachycardia in six weeks. The fourth type of cardiac rhythm occurred during the early stage of atropine action (six minutes after injection), and was described by Wilson as a low nodal rhythm, in contradistinction to the other, or high nodal, type. He attributed these changes to migration of the pacemaker caused by vagus action.

In 1930, Wolff, Parkinson, and White[3] described a syndrome of "bundle branch block with short P-R interval" in healthy young people who were prone to paroxysmal tachycardia, auricular fibrillation, or even auricular flutter. These patients usually regained normal rhythm spontaneously, either with exercise or by the action of atropine. These authors suggested the possibility of a congenital anomaly in the conduction system, but felt that the syndrome was probably the result of vagus action.

Holzman and Scherf[4] and Wolferth and Wood,[5] independently, presented the hypothesis that this syndrome is caused by an accessory pathway of auriculoventricular conduction. Wolferth and Wood presented the following reasons in support of their view: (1) The interval from the beginning of the P wave to the end of the QRS deflection is normal. (2) This interval was the same in the normal complex and the abnormal complex; a change occurred only in the P-R interval. (3) Slurring involved only the initial deflection of the QRS. They concluded that this was not bundle branch block, but the manifestation of an *early arrival* in the ventricle of the impulse from the auricle. They showed that a functioning bundle of Kent would account for all of the phenomena of this syndrome: (a) The P-R interval was short because the pathway was short. (b) Premature invasion of a section of the ventricular musculature would cause slurring of the initial deflection of QRS and widening of QRS at the expense of the P-R interval. (c) Conductivity through the bundle of Kent may be slow, so that it may fail to function when impulses are formed at a rapid rate. (d) Auricular paroxysmal tachycardia and fibrillation may be caused by retrograde conduction in the bundle, which was shown to occur in rats by Kent.

In 1936, Cossio, Berconsky, and Kreutzer[6] advanced the theory that the abnormal complexes originate from a hyperirritable ventricular focus, and that this focus is irritated by the action of auricular systole.

In the same year, Tung[7] presented two cases and expressed the opinion that the entire syndrome was the result of a change in vagal tone.

In 1937, Bishop[8] reviewed the literature and found that the effect of atropine and exercise was not constant. This was evidence against the theory of vagus influence. The second theory, that of an aberrant conduction bundle, was discarded merely because such an anomaly had never been demonstrated in a patient with this syndrome.

In 1938, Moia and Inchauspe[9] presented a case of this syndrome and noted absence of Q in Lead IV (old technique), absence of axis deviation, and T waves in a direction opposite to QRS. A strip of Lead II showed abnormal complexes with occasional normal beats; there was coupling for several beats, but no regular bigeminy.

In 1940, Hunter, Papp, and Parkinson[10] reviewed this subject and suggested that the abnormal complexes may be explained as the result of double rhythm by two interfering pacemakers.

In 1941, Wolferth and Wood[11] re-examined this subject and presented further evidence in support of their original hypothesis.

In 1942, Butterworth and Poindexter[12] reported two cases in which auricular premature beats were followed by abnormal ventricular complexes. This was in refutation of several theories, especially that of double rhythm caused by two interfering pacemakers. They also presented experimental work in which, by means of an amplifier, the electrical impulses from the auricle were conducted to the ventricle *before* the impulse arrived normally through the auriculoventricular conduction system. This produced typical electrocardiographic tracings, with short P-R interval and prolonged QRS complexes. Reversal of the flow, from ventricle to auricle, caused typical auricular tachycardia. This demonstration lent weight to the theory of Wolferth and Wood regarding retrograde conduction in the bundle of Kent as a cause of the paroxysms of auricular tachycardia.

Wood, Wolferth, and Geckeler,[13] in 1943, obtained an autopsy on a patient who had had this syndrome. They found an accessory bundle exactly where it was described by Kent.

In 1925, it was realized that paroxysmal tachycardia occurred with certain other diseases too often to be considered merely coincidental. Laubry and Mussio-Fournier[14] reported seven cases of both asthma and paroxysmal tachycardia; Thomas and Post[15] wrote of the frequent occurrence of paroxysmal tachycardia in cases of migraine, and suggested that the tachycardia might be an unusual manifestation of this disease.

It was not until four years later that Luria and Wilensky[16] first postulated that paroxysmal tachycardia is an allergic disease. The following year, they[17] presented the case of a woman with mitral valvular disease who was subject to attacks of paroxysmal tachycardia. These

attacks would occur immediately after eating raisins and honey. Skin tests with apple, starch, raisin, and honey showed positive reactions to raisin and honey. Elimination of these foods from the diet resulted in cessation of the attacks.

In 1932, Weill[18] referred to the work of Luria and Wilensky[17] and reported six cases in which paroxysmal tachycardia was associated with asthma, urticaria, and other allergic phenomena. He stated that paroxysmal tachycardia was not always allergic, but felt that allergy was a definite factor in some cases. One patient had migraine, eczema, and paroxysmal tachycardia. She ate chocolate constantly while working, and consumed an enormous quantity. Upon the removal of chocolate from her diet, the attacks of migraine and tachycardia almost, but never completely, disappeared.

In the same year, Mussio-Fournier[19] referred to his original article and presented further evidence in favor of the idea that allergy may be a factor in paroxysmal tachycardia.

In 1937, Gay[20] referred to cases in which paroxysmal tachycardia was controlled by eliminating certain foods from the diet; the tachycardia recurred when these foods were again eaten.

Kern[21] stated that paroxysmal auricular tachycardia is perhaps the most outstanding cardiac disorder in which allergy may play a part.

DISCUSSION

This case is presented because of the unusual electrocardiograms, the unusual reaction to exercise, and the possibility that the precipitation of the paroxysmal tachycardia might have been an allergic manifestation.

ELECTROCARDIOGRAMS

1. With a slow rate, there was marked sinus arrhythmia, all of the complexes were abnormal, and the QRS complexes were of greater amplitude and less slurred than when the rate was more rapid.

2. With increase in rate after exercise or atropine, the typical patient with this syndrome would show a return to normal rhythm, but in this case it was impossible to produce a single normal complex by causing an acceleration of the rate. When the rate was increased to over 90, the sinus arrhythmia disappeared. The QRS complexes were of lower voltage and the notching was more evident.

3. With the fast rate preceding or following an attack of paroxysmal tachycardia, normal complexes were frequently seen together with abnormal complexes; in none of the tracings were all of the complexes normal. The mechanism of these changes is highly problematical, and will not be discussed in this paper, except to say that, when bigeminy was present, it was evident that the cardiac impulses alternated between the normal bundle and the bundle of Kent. From the practical standpoint, it should be noted that the tracing in Fig. 3 showed a constant

bigeminal rhythm.* If this were the only tracing available, one could not be criticized for failing to make the correct diagnosis. This should teach us that multiple tracings are required whenever the underlying mechanism is not perfectly clear.

4. It is interesting that the only time normal complexes occurred was immediately before or after a paroxysm of tachycardia. With the theory of Wolferth and Wood and the experimental evidence of Butterworth and Poindexter in mind, might this not mean that an occasional *normal* complex initiates an impulse which re-enters the auricle through the bundle of Kent and there sets up a paroxysm of tachycardia?

5. In cases of typical supraventricular paroxysmal tachycardia, carotid sinus pressure, if effective at all, will cause the tachycardia to disappear entirely. Such was not the case in this patient; sustained pressure caused the tachycardia to cease for several beats, after which it was resumed.

ALLERGIC STUDY

1. Inasmuch as the syndrome of short P-R interval and prolonged QRS complex, associated with paroxysms of tachycardia, is well recognized, it seems far fetched to look upon allergy as a cause of these attacks.

2. I have seen one patient with this syndrome (discovered on routine examination) who regained normal rhythm after exercise and had never had an attack of tachycardia.

3. Although allergy is probably not always a factor in this syndrome, it is reasonable to suppose that it may act as a precipitating cause of some of the paroxysms of tachycardia which these patients have. This particular patient had about one attack every three weeks prior to his entrance into the hospital. When he began to drink soft drinks instead of beer, he had attacks much more often. His skin tests (and passive transfer reactions) showed strong reactions to cane sugar and a few other common foods. On two occasions, after the patient had been on a diet of lamb, rice, and milk, the addition of cane sugar was followed by an attack. When the patient was placed upon a diet which eliminated all foods to which he was sensitive, the attacks became less frequent and the patient was much more comfortable.

4. It is hoped that this report will serve to stimulate interest in the possible allergic aspects of this syndrome.

SUMMARY

1. A case in which the electrocardiogram showed a short P-R interval and a prolonged QRS complex, together with several unusual features not reported previously, is presented.

*Thorough search of the literature failed to reveal any publication or description of such a tracing. The only similar record is one published by Moia and Inchauspe," which differed in that it never showed regular alternation or a constant bigeminal rhythm. Alternation between normal and bundle branch block complexes should not be confused with this type of tracing.

2. The possibility that food allergy may have precipitated some of the attacks of paroxysmal tachycardia is considered.

The study of this case from the allergic standpoint was conducted by Lieutenant Harry Swartz.

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THE PERIPHERAL BLOOD FLOW UNDER BASAL CONDITIONS IN NORMAL MALE SUBJECTS IN THE THIRD DECADE

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THERE has been increasing interest in recent years in that part of the total cardiac output which is allocated to the peripheral circulation. Contributions to our knowledge of peripheral blood flow have been stimulated by increasing attention to inflammatory, occlusive, and vasospastic states of the peripheral vessels. Most of the data relating to the amount of the peripheral circulation have been derived from changes in the volume of an extremity or digit, or in the temperature of an extremity. During the past four years we have used a method by which measurement of the amount of blood allotted to the periphery of the body can be made in health and disease, as well as to estimate the effect of drugs on this part of the circulation.[1-7] During the course of these investigations we have accumulated data on the average peripheral blood flow in a group of normal persons between the ages of 20 and 30 years.

The peripheral blood flow has now been studied seventy-five times on thirty-four male subjects who, from physical examination, could be designated as normal. All were approximately 20 to 30 years of age, and most of them were members of the house staff of the New York Hospital or medical students from Cornell University Medical College.

METHOD

Measurements of the peripheral blood flow were made by modifying the method of Hardy and Soderstrom[8] in such a way that observations could be carried out without the use of a calorimeter. This modification has been described elsewhere.[1, 2, 6] In order to use this method, certain data were required, namely, skin temperatures at eleven points on the anterior surface of the body,[1] rectal temperature, oxygen consumption, height, and body weight. In addition, the blood pressure and pulse rate were recorded.

The skin temperatures were measured with the improved Hardy-Soderstrom radiometer,[9] the rectal temperature with a single-junction, copper-constantan thermocouple,[9] and the oxygen consumption with a Benedict-Roth metabolism apparatus.[10] The basal metabolic rate was calculated from the Mayo Foundation standards for age and sex,[11] and the surface area from the tables of DuBois and DuBois.[12]

PROCEDURE

All of the observations were made in the morning, when the subjects were in a basal metabolic state. The rectal thermometer was inserted to a depth of about 10 cm. as soon as the subjects came to the constant temperature room, and remained in place throughout the morning. The subjects lay nude in bed covered

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only by a sheet. The studies were made at the temperatures which we have most frequently employed, namely, 25° C. and 27° C. The relative humidity was maintained between 30 per cent and 50 per cent. The subjects adjusted to the environment of the constant temperature room for at least an hour before the observations were begun.

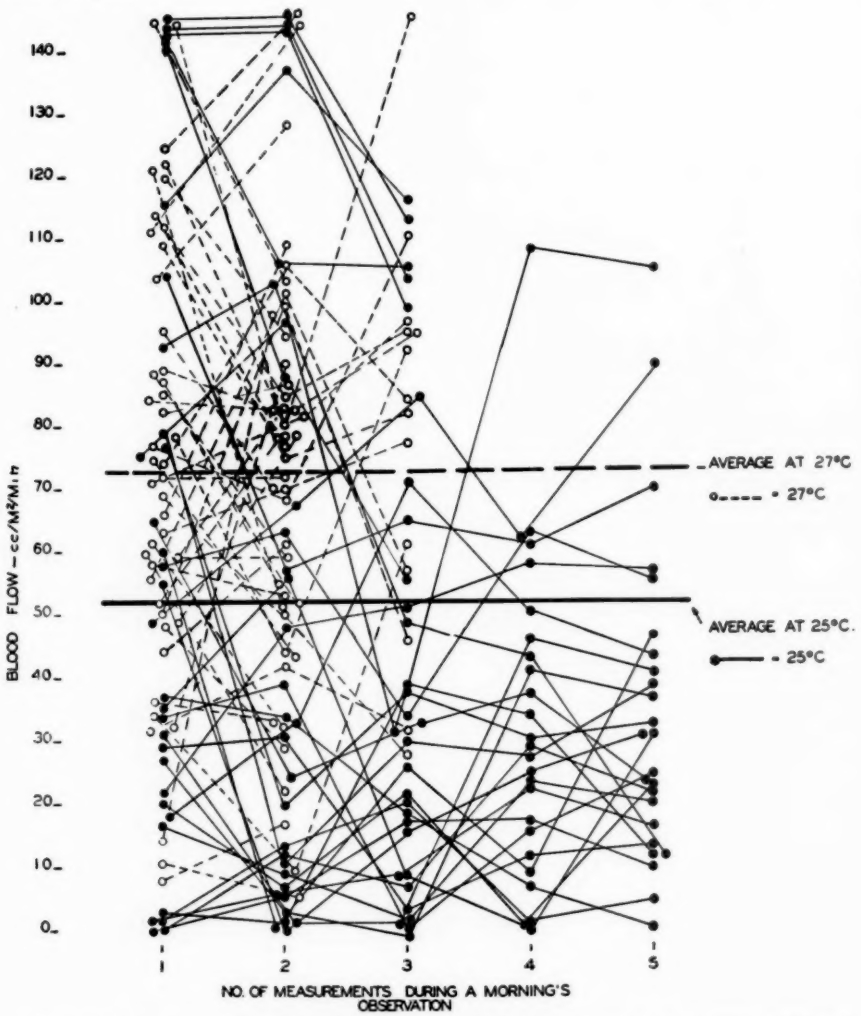

Fig. 1.—This figure shows all of the individual measurements of average peripheral blood flow on all subjects during the course of a morning's observations. Those made at a room temperature of 25° C. are plotted as closed circles, and those at a room temperature of 27° C. are shown as open circles. For the most part, the peripheral blood flow was greater at the higher room temperature.

The data were collected in the following order: First, the oxygen consumption was measured. The room temperature was then noted, after which the temperatures of the skin of the eleven areas[1] were recorded. The rectal temperature was next measured. Six sets of skin and rectal temperatures were recorded on some subjects, and three to four sets on others. The interval between temperature readings was ten minutes in some cases and twenty minutes in others. The average peripheral

blood flow per minute during the ten- or twenty-minute intervals was calculated, and is shown in Fig. 1. This flexibility was permissible, for the final calculations of peripheral blood flow were made on the basis of c.c./M²/Min. The blood pressure and pulse rate were recorded during free intervals between temperature readings. After obtaining the required number of sets of skin and rectal temperature, the oxygen consumption was measured again.

OBSERVATIONS

The results of observations at a room temperature of 25° C. are shown in Table I, and those at 27° C. in Table II.

Peripheral Blood Flow.—The trends of the peripheral blood flow during the course of a morning's observation are shown in Fig. 1. During an observation, the peripheral blood flow in any one subject showed fluctuations. Also, in successive observations on the same subject, a variation was observed. Although there is overlapping in values at the two temperatures, nevertheless it is apparent that, for the most part, at 27° C. the peripheral blood flow was greater than at 25° C. In one subject (No. 25, G. V., Table I), the peripheral blood flow with the room temperature at 25° C. was, on the six occasions when it was measured, 97 to 163 c.c./M²/Min.—that is to say, greater than all the others of this group, in which the next highest was 78 c.c./M²/Min. The basal metabolic rate was consistently in the lower range. We have no explanation for the fact that this subject's peripheral blood flow was so far out of line with the others in this group.

In two subjects (No. 8, M. McC., and 11, W. L., Table II), at the higher room temperature (27° C.), the peripheral blood flow was much less than that of all of the others of this group. Their basal metabolic rates were in the low range, but others in the group with lower basal metabolic rates had a greater peripheral blood flow, so that this is probably not the explanation for their low values.

In four subjects (No. 1, L. E., 6, R. T., 12, C. H., and 13, J. S., Table II, and subjects No. 5, L. E., 1, R. T., 22, C. H., and 7, J. S., Table I, respectively), the peripheral blood flow was measured at 27° C. as well as at 25° C., and was greater at the higher room temperature.

The average peripheral blood flow for all subjects was 52 c.c./M²/Min. at a room temperature of 25° C., and 73 c.c./M²/Min. at a room temperature of 27° C. That is to say, the peripheral blood flow was 21 c.c./M²/Min. greater at the higher room temperature (Tables I and II).

Basal Metabolism.—The average basal metabolic rate at 25° C. was minus 6 per cent. In this group the highest basal metabolic rate was plus 15 per cent, and the lowest, minus 18 per cent (Table I). The average at 27° C. was minus 5 per cent. The highest basal metabolic rate in this group was plus 20 per cent, and the lowest, minus 23 per cent (Table II). When more than one set of observations was made on a subject, slight variations in oxygen consumption were observed from day to day (Tables I and II). Approximately 60 per cent of the

TABLE I

DATA RELATING TO 25 NORMAL MALE SUBJECTS AT A ROOM TEMPERATURE OF 25° C.

SUBJECT NUMBER		DATE	PERIPHERAL BLOOD FLOW C.C./M²/MIN.	AVERAGES OF						
				BASAL METABOLIC RATE %	RECTAL TEMP. °C.	SKIN TEMP. °C.	HAND TEMP. °C.	FOOT TEMP. °C.	BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.
1.	R. T.	6/10/41	23	−14	36.49	32.19	32.9	28.9	115/81	61
2.	J. S.	6/11/41	71	+4	36.53	33.17	34.1	33.9	113/78	73
3.	A. R.	6/12/41	47	0	36.82	33.21	33.8	29.9	110/70	60
4.	F. E.	6/18/41	14	−12	36.60	32.41	32.6	27.7	96/60	59
5.	L. E.	6/20/41	36	−5	36.73	32.72	33.6	30.4	98/66	48
6.	L. L.	2/21/41	22	+15	37.26	32.84	33.3	28.4	117/70	64
7.	J. S.	6/23/41	38	−11	36.85	33.26	34.5	33.6	105/70	68
8.	R. M.	6/24/41	18	−9	36.42	32.75	33.9	31.5	104/74	48
9.	F. McN.	6/26/41	19	−18	36.58	32.74	32.7	30.9	98/68	65
10.	A. P.	6/27/41	8	−18	36.87	32.43	33.6	28.8	112/74	52
11.	W. McD.	6/28/41	55	−1	36.65	33.23	34.6	33.4	109/60	68
12.	B. V.	6/30/41	39	+1	36.90	32.98	33.3	29.6	109/71	56
13.	G. D.	7/ 5/41	14	−5	36.71	32.86	34.4	32.7	117/81	64
14.	C. L.	7/ 9/41	14	−4	37.07	32.53	32.8	27.1	108/71	56
15.	R. O.	7/10/41	10	−1	37.06	32.68	33.2	28.1	116/78	61
16.	T. R.	7/11/41	18	−12	36.65	32.89	33.8	32.6	100/70	63
17.	J. B.	7/12/41	11	−17	36.69	32.71	33.9	31.9	98/68	56
18.	A. M.	7/30/41	26	−7	36.37	32.39	33.6	30.2	106/76	60
19.	S. H.	7/16/41	28	−11	36.77	32.41	33.1	31.5	112/68	52
20.	J. F.	7/17/41	24	−3	36.84	32.79	32.8	30.0	124/74	65
21.	C. S.	7/29/41	84	+5	36.55	33.39	34.3	32.7	107/69	47
22.	C. H.	7/21/41	37	−5	36.66	32.92	34.2	32.4	102/70	58
23.	K. D.	7/25/41	43	−5	36.62	33.22	34.0	33.2	116/74	60
24.	T. H.	7/15/41	78	+11	36.76	33.32	34.0	32.8	107/70	56
		7/19/41	51	+3	36.72	32.40	32.9	30.6	101/69	56
25.	G. V.	2/17/42	119	−11	36.43	33.50	33.5	33.0	101/57	48
		2/18/42	97	−18	36.24	33.79	33.9	32.5	97/62	49
		2/19/42	163	−6	36.28	34.08	34.3	33.7	99/66	52
		2/21/42	122	−12	36.11	33.77	34.5	33.9	100/62	52
		3/10/42	134	−14	36.42	33.76	34.2	33.5	100/64	48
		3/12/42	140	−4	36.44	33.90	34.8	34.0	100/64	56
Group Averages			52 c.c.	−6%	36.64° C.	33.01° C.	33.7° C.	31.4° C.	106/70	57

subjects in both groups showed a slight increase in basal metabolic rate during a morning's observations, and 40 per cent showed a decrease. This is not apparent in Tables I and II, however, in which the average rate for the morning's experiment is recorded.

Rectal Temperature.—The average rectal temperature with the room at 25° C. was 36.64° C., and, at 27° C., it was 36.79° C.; that is to say, it was slightly higher at the higher room temperature (Tables I and II). The lowest rectal temperature with the room at 25° C. was 36.11° C., and the highest, 37.26° C. (Table I). At 27° C. the lowest rectal temperature was 36.32° C., and the highest, 37.24 C. (Table II). Small variations in rectal temperature were observed from day to day among those subjects upon whom several measurements were made (Tables I and II).

Skin Temperature.—The average skin, hand, and foot temperatures with the room at 25° C. were 33.01° C., 33.7° C., and 31.4° C., respectively (Table I). The average skin, hand, and foot temperatures at 27° C. were 33.75° C., 34.4° C., and 32.7° C., respectively (Table II). In short, the skin temperatures were higher at the higher room temperature. When more than one set of observations was made on a subject in either group, the average skin, hand, and foot temperature varied from day to day. The highest average foot temperature was recorded at the highest room temperature (E. B., 3/2/42; F. H., 9/29/41; and R. T., 10/30/41, Table II). On the other hand, the lowest individual average foot temperature (26.0° C.) was recorded at the higher room temperature (R. B., 1/21/41, Table II). The highest and lowest individual average skin and hand temperatures were always greater at the higher room temperature.

Blood Pressure and Pulse Rate.—The average systolic and diastolic blood pressures were the same at 25° C. as at 27° C. There was a slight difference in average pulse rate, which was 57 per minute at 25° C. and 61 per minute at 27° C. (Tables I and II). Neither the blood pressure nor pulse rate varied significantly from day to day in any one subject (Tables I and II).

DISCUSSION

The average peripheral blood flow was 52 c.c./M²/Min. with the room temperature at 25° C., and 73 c.c./M²/Min. at 27° C. (Tables I and II, Fig. 1). That is to say, the average peripheral blood flow bears a direct relationship to environmental temperature, for the blood flow was 21 c.c./M²/Min. greater at the higher room temperature. These results are in agreement with those of Hardy and Soderstrom[8] and Hick, Keeton, Glickman, and Wall.[13] However, when each individual in each group was considered, the variation in blood flow was such that values for certain subjects at one temperature overlapped those at the other (Tables I and II, Fig. 1). In addition, when several observations were carried out on a subject, the peripheral blood flow varied from one day

TABLE II

DATA RELATING TO 14 NORMAL MALE SUBJECTS AT A ROOM TEMPERATURE OF 27° C.

SUBJECT NUMBER	DATE	PERIPHERAL BLOOD FLOW C.C./M²/MIN.	AVERAGES OF						
			BASAL METABOLIC RATE %	RECTAL TEMP. °C.	SKIN TEMP. °C.	HAND TEMP. °C.	FOOT TEMP. °C.	BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.
1. L. E.	9/10/41	87	−10	36.64	33.77	34.1	32.4	105/64	55
	11/16/41	72	−13	36.55	33.80	34.2	33.3	112/61	43
	1/ 9/42	56	−10	37.00	34.16	34.4	32.8	105/60	50
	5/19/42	71	−5	36.80	33.75	34.4	33.7	102/62	53
2. E. B.	2/24/42	70	−4	36.89	33.90	34.6	33.5	101/68	69
	2/26/42	49	−10	37.15	33.79	34.9	33.9	107/80	69
	3/ 2/42	119	+2	37.02	34.21	35.0	34.3	102/72	71
	3/ 3/42	85	0	37.07	33.86	34.8	34.2	106/73	70
	3/ 4/42	67	+5	36.74	33.80	34.6	34.0	109/70	60
	3/ 7/42	97	+12	36.36	33.28	34.1	33.8	106/70	62
	3/18/42	69	−12	36.93	33.94	34.6	34.2	102/68	66
3. R. B.	1/21/41	39	+1	37.10	33.41	33.8	26.0	106/70	60
	3/21/42	89	+3	37.24	33.71	34.5	28.9	106/71	65
	5/23/42	35	−10	36.86	33.06	33.9	29.6	100/70	62
4. W. S.	8/ 6/41	82	0	37.09	33.38	34.1	31.5	121/81	71
	1/ 3/42	93	−10	36.61	33.66	34.3	33.0	114/73	71
	2/12/42	83	−12	36.32	32.65	32.8	32.5	111/75	55
	5/20/42	35	−15	36.60	33.34	34.1	33.2	105/71	54

5.	F. H.	9/ 5/41	77	−3	36.79	33.87	34.6	33.5	112/67	56
		9/29/41	54	+1	36.75	33.84	35.1	34.3	103/69	61
		10/27/41	72	+1	36.48	33.36	34.3	33.5	95/69	42
		11/15/41	46	-2	36.81	33.67	34.6	32.9	94/62	59
		12/ 5/41	113	+2	36.91	34.05	34.3	33.0	101/68	64
		12/ 6/41	157	+5	36.68	33.91	34.5	33.8	106/70	61
		12/ 9/41	71	-6	36.48	33.83	34.7	33.9	109/71	59
		12/18/41	41	+8	37.01	33.15	34.4	33.6	103/69	56
		1/ 3/42	41	−5	36.62	33.28	34.2	33.8	103/71	59
		1/12/42	67	−4	36.86	33.74	34.9	34.2	101/69	56
		2/ 7/42	91	+4	36.92	34.00	34.9	34.2	103/67	61
6.	R. T.	10/28/42	60	−19	36.58	33.70	34.7	34.2	114/73	65
		10/30/41	108	−10	36.64	33.82	34.8	34.3	108/69	59
		11/11/41	86	−18	36.61	33.93	34.7	34.0	111/70	60
7.	F. D.	9/11/41	61	−13	36.73	33.77	34.0	32.6	103/70	57
		9/30/41	126	−6	36.69	34.26	34.6	33.8	109/74	57
		10/22/41	116	−5	36.87	34.18	34.6	34.1	107/73	60
8.	M. McC.	9/18/41	13	−23	36.87	33.37	33.5	31.8	101/64	60
		2/22/42	87	−19	36.79	33.50	34.0	28.6	97/58	65
		2/25/42	83	−19	36.79	34.25	33.8	30.5	96/65	59
9.	G. W.	10/29/41	34	0	36.77	33.80	33.3	29.6	105/63	54
10.	R. B.	1/25/41	134	+20	36.86	34.35	34.5	33.5	105/73	76
11.	W. L.	10/31/41	8	−2	36.98	33.25	33.2	27.3	108/77	67
12.	C. H.	1/24/41	63	−8	36.81	34.25	35.1	34.2	99/66	64
13.	J. S.	2/ 1/41	56	−16	36.57	34.36	34.8	33.9	107/71	64
14.	W. B.	12/30/41	71	−1	36.95	34.18	35.5	30.6	97/65	64
Group Averages			73 c.c.	−5%	36.79° C.	33.75° C.	34.4° C.	32.7° C.	105/71	61

to the next (Tables I and II, Fig. 2*a* and 2*b*). Although there were variation and overlapping in values, the peripheral blood flow tended for the most part to be greater at the higher room temperature (Fig. 1). These data show, therefore, that the peripheral blood flow did not lie within narrow limits, among different subjects in the same age and temperature group, or in the same person. This was not unexpected, for, although all of the observations were made under the same conditions, many factors, such as emotion, metabolic requirements of the tissues, and the amount of subcutaneous fat, determine how much of his total basal cardiac output each person must allot to the periphery.

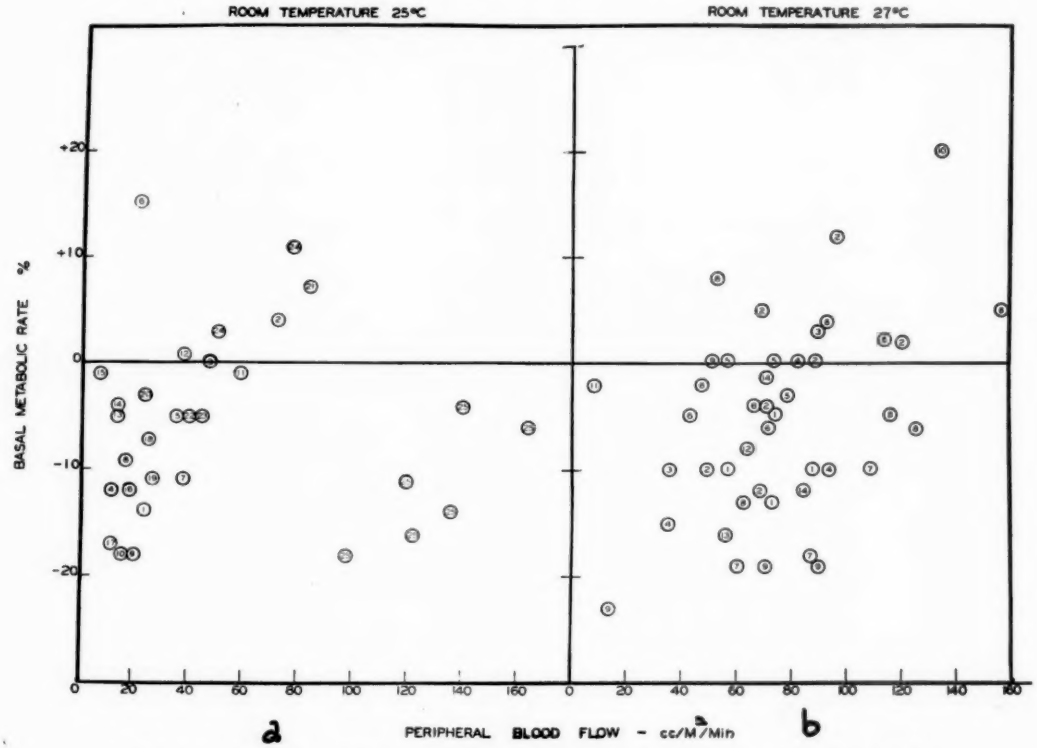

Fig. 2.—In this figure the data for peripheral blood flow are plotted against the corresponding basal metabolic rates at 25° C. and 27° C., respectively. A linear relation is established, for with an increase in basal metabolic rate the peripheral blood flow also increases. The numbers in the circles refer to subjects in Tables I and II. In the observations made at 25° C. we have no explanation for the dislocation of subject 25 from the rest of the group.

The average basal metabolic rate was the same for both groups of subjects; that is to say, it was minus 6 per cent at 25° C. and minus 5 per cent at 27° C. (Tables I and II). The highest and lowest basal metabolic rates in the two groups were essentially the same, i.e., plus 15 per cent and minus 18 per cent, respectively, at 25° C., and plus 20 per cent and minus 23 per cent, respectively, at 27° C. (Tables I and II). When more than one set of observations was carried out on

one subject, small variations in basal metabolism were observed from day to day. Approximately 60 per cent of the measurements in both groups showed small increases in oxygen consumption at the end of a morning's observation, and 40 per cent showed small decreases in basal metabolic rate. This is not apparent in Tables I and II because they show the average of all the basal metabolic rates for the morning's experiment. Benedict and Campbell[14] were unable to detect from their data on a large number of subjects any definite change in oxygen consumption during a morning's observation. Furthermore, DuBois[15] could find no consistent change in basal metabolism during the day. Although our subjects lay quietly in the basal metabolic state, certain observations were being made upon them, i.e., skin temperatures were taken over the anterior surface of the body at certain intervals and blood pressures and pulse rates were recorded. The tendency for the oxygen consumption to increase slightly in 60 per cent of the measurements during a morning's observation was probably of no significance. On the whole, there was a rough linear relationship between the amount of peripheral blood flow and basal metabolic rate, for, at both 25° C. and 27° C. room temperature, there was a gradual increase in peripheral blood flow from those with the lower basal metabolic rate to those with the higher metabolic rate (Fig. 2a and 2b). This relationship between basal metabolic rate and peripheral blood flow was much more apparent in the patients with myxedema[5, 6] and hyperthyroidism[2] who were studied by Stewart and Evans (Fig. 2a and 2b).

The group averages of rectal, skin, hand, and foot temperatures were higher at the room temperature of 27° C. than they were at 25° C. (Tables I and II). Analysis of Tables I and II shows that the average rectal temperature of the subjects who were studied at 27° C. was only 0.15° C. higher than that of those who were studied at 25° C. On the other hand, the average skin temperature was increased 0.74° C. by the higher room temperature. These observations serve to illustrate two points: In the first place, Hardy and DuBois[16] have shown that the average skin temperature increases about 0.5° C. for each 1.0° C. rise in environmental temperature. They made observations on their subjects in the Russell-Sage Calorimeter. Although a calorimeter was not employed by us, our results show close agreement with those of Hardy and DuBois;[16] the average skin temperature of our subjects increased 0.37° C. for each 1.0° C. rise in room temperature (Tables I and II). The slight difference in average rectal temperature at the two room temperatures brings out the second point. Although there was a difference in environmental temperature of 2.0° C. between the two groups, the adjustments of human heat regulation were such that the average for the internal temperature of both groups of subjects was approximately the same. The constancy of internal temperature may have been brought about by loss of heat through increased allotment of

blood to the surface, for the average peripheral blood flow was 21 c.c./M²/Min. higher at the higher room temperature (Tables I and II).

In those subjects upon whom more than one observation was made, the average internal and surface temperatures varied from one day to the next. In addition, these data and those of single observations show that the highest skin temperature did not always occur with the higher rectal temperature, and the warmest hands and feet were not always associated with the warmest skin (Tables I and II). It becomes apparent, therefore, that no direct relationship existed between any of the individual local temperatures.

The blood pressures and pulse rates of all the subjects were normal. Small variations which occurred from day to day in the same subject were of no significance.

SUMMARY

By means of a method which has been employed by us in other studies,[1-7] seventy-five measurements of the peripheral blood flow in c.c./M²/Min. were made on thirty-four normal male subjects. In addition, the basal metabolic rates, blood pressures, and pulse rates were recorded. The results may be summarized as follows:

1. The peripheral blood flow under basal conditions at 25° C. room temperature showed a range from 8 to 78 c.c./M²/Min. in all instances except one, in which it was consistently higher. Peripheral blood flow was usually less with a lower basal metabolic rate and greater with a higher basal metabolic rate. The average for all subjects at this temperature was 52 c.c./M²/Min.

The peripheral blood flow of the subjects who were studied at 27° C. room temperature ranged from 34 to 157 c.c./M²/Min. except for two instances, in which it was 8 and 13 c.c./M²/Min., respectively. Again, the peripheral blood flow usually varied in the same direction as the basal metabolic rate. The average for all subjects at this temperature was 73 c.c./M²/Min.

There was overlapping of the level of peripheral blood flow at the two room temperatures, but, on the average, the flow was greater at the higher temperature. In four subjects who were studied at both room temperatures, the peripheral blood flow was greater at the higher room temperature.

2. The average basal metabolic rate was the same in the two groups; that is to say, it was minus 6 per cent at 25° C., and minus 5 per cent at 27° C. Small increases in basal metabolism were recorded in 60 per cent of the experiments at the end of a morning's observations, and small decreases in 40 per cent. These changes were not of sufficient magnitude to be considered significant.

3. The average rectal, skin, hand, and foot temperatures were higher at the higher room temperatures (27° C.). The increase in average surface temperature was approximately 0.4° C. for each degree rise in

room temperature. At the same time, the average rise in rectal temperature was small. This constancy in rectal temperature appears to have been brought about by the allocation of more blood to the surface of the body at the higher room temperature.

4. The blood pressure and pulse rate were normal in each instance, and there were essentially no differences in the averages for the subjects who were studied at 25° C. and those at 27° C.

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THE EFFECT OF SMOKING CIGARETTES ON THE PERIPHERAL BLOOD FLOW

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THE effects of the smoking of tobacco on the peripheral vascular system has been the subject of many investigations in recent years. Using the fall in finger temperature as an index of decreased peripheral blood flow, Maddock and Coller[1] have shown in man that the effects of smoking standard cigarettes could be reproduced by the intravenous injection of 1.0 mg. of nicotine. Haag[2] demonstrated in animals that the vasoconstriction and rises in blood pressure occasioned by the intravenous injection of smoke solutions were proportional to their nicotine content. Wright and Moffat[3] observed decreases in the finger-tip and toe-tip temperatures and vasoconstriction of the capillary loops of the nail fold, and concluded that there were no appreciable differences between the effects of standard cigarettes and cigarettes which contained only 40 per cent as much nicotine. In Wright and Moffat's experience,[3] as well as in that of Maddock and Coller,[1] smoking cigarettes which contained no nicotine was associated with only negligible changes.

Mulinos and Shulman[4] employed the capillary microscope, the plethysmograph, and the skin temperature in a correlation of the changes that occurred in the extremities as the result of smoking and deep breathing. They likewise found no difference in the effects of tobacco cigarettes of varying strengths. Moreover, they were of the opinion that the greater part of the observed decrease in peripheral blood flow could be accounted for by deep breathing. Abramson, Zazeela, and Oppenheimer,[5] who made plethysmographic studies of the hand, forearm, and foot, concluded that smoking probably causes decreased blood flow in the skin and not in the voluntary muscle. There is, therefore, confusion about the effect that tobacco has on the peripheral blood flow.

Observations on the peripheral blood flow in all of these studies,[1-5] as pointed out, were based upon changes in the volume of an extremity as recorded by modified plethysmographs, on inferences about blood flow from changes in the skin temperature of an extremity, or on direct observation of the capillary loops of the nail fold. Since a relatively new method was available for the measurement of peripheral blood

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flow,[6] it seemed worth while to reinvestigate the effects of the smoking of tobacco, and make a comparison with cigarettes which contained *no* nicotine.

In the study now being reported, all of the subjects smoked regular (standard) cigarettes, commercially denicotinized cigarettes, and cigarettes made from cornsilk. Cornsilk was selected as a control substance because it contains no nicotine. Four observations were made on three of the subjects to secure data concerning the effect of fully denicotinized cigarettes.* In addition, two of the subjects smoked cigarettes through a water pipe. Measurements of the peripheral blood flow were made before, during, and after smoking. Ten normal male subjects whose ages ranged from 19 to 36 years were selected for study. Most of the subjects were physicians from the house staff of the New York Hospital.

METHOD

The measurements of peripheral blood flow were made by means of a modification[6] of the method of Hardy and Soderstrom.[7] Hardy and Soderstrom have shown that, at temperatures below 28° C., the skin functions like a dead insulator when the subject is lying nude in the basal state, and that blood flow to the skin, thermal conductivity of the peripheral tissues, and vaporization are constant and minimum. With an increase in blood flow to the periphery, more heat is brought from the deeper tissues to the surface; this increases the thermal conductance of the superficial tissues, and, therefore, changes in thermal conductance become an index to peripheral blood flow. With this method, blood flow is expressed as a function of heat loss, surface area, *average skin temperature,* and rectal temperature. The method requires the recording of skin and rectal temperatures at known intervals, and of oxygen consumption, height, and body weight. The skin temperatures were recorded with a Hardy-Soderstrom radiometer from 11 points on the anterior surface of the body. With this method the amount of blood allocated to the whole periphery of the body is measured, rather than the flow in local areas, and may be expressed as c.c./M²/Min. In addition, the blood pressures and pulse rates were recorded between temperature readings. Electrocardiograms, including Lead IV F, were taken immediately before and during the smoking of the various types of cigarettes.

PLAN OF PROCEDURE

The plan of procedure was essentially the same as that described in a recent publication.[6] In the present study, measurements of skin and rectal temperatures were made at ten-minute intervals instead of at twenty-minute intervals, as in previous work. Each set of measurements covered ninety minutes. The blood pressures and pulse rates were recorded during free intervals between temperature readings. The basal metabolic rate was measured before smoking, immediately after smoking, and again at the end of a morning's observations. For the period before smoking the first basal metabolic rate was used in the calculation of peripheral blood flow. For the period during smoking the average of the oxygen consumption before and immediately after smoking was used for calculating peripheral blood flow. For the phase after smoking, the difference between the oxygen consumption immediately after smoking and that at the conclusion of the experiment was divided by the

*We wish to thank Dr. Harvey B. Haag, Professor of Pharmacology, Medical College of Virginia, Richmond, Va., for generously furnishing the authors with fully denicotinized cigarettes.

number of periods of peripheral blood flow measurements in such a way that it was properly apportioned among these periods. One type of cigarette was smoked during a morning's observations. Only those subjects were chosen who were accustomed to smoke and inhaled while smoking. The subjects smoked, in succession, two-thirds of two cigarettes at their normal inhalation depth and frequency; exaggerated smoking was avoided. The duration of smoking varied with the subjects from sixteen to eighteen minutes. A room temperature of 27° C., with a relative humidity of approximately 40 per cent, was maintained. The cigarettes, whether regular (standard) or commercially denicotinized, were of the

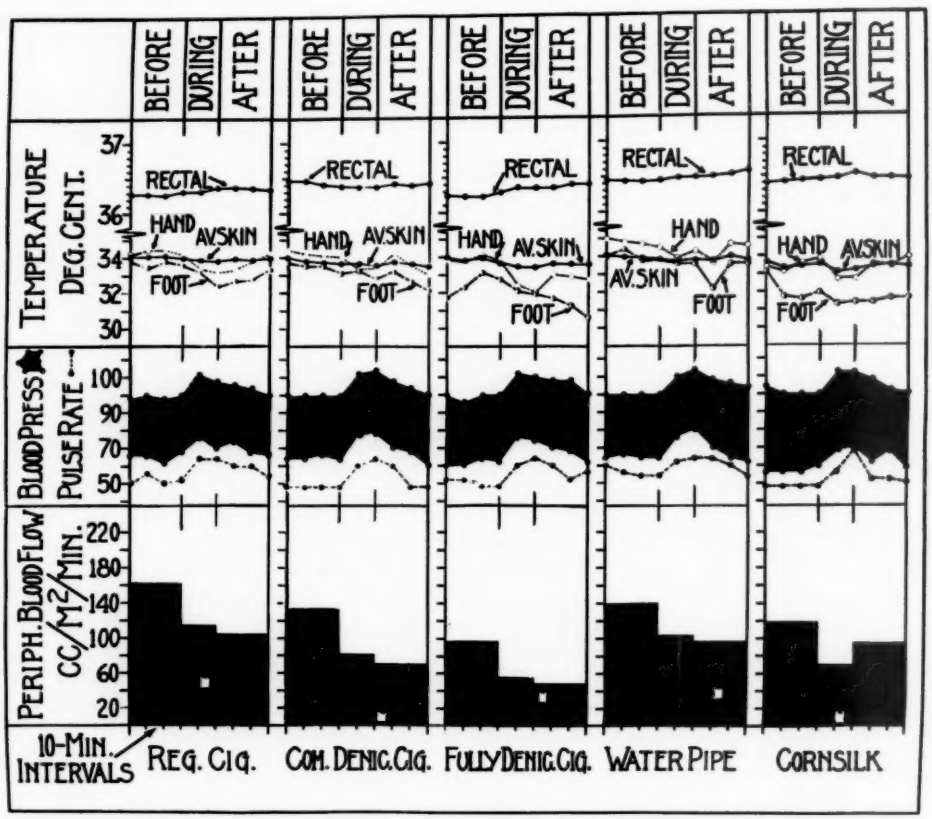

Fig. 1.—Data relating to the effect of smoking different types of cigarettes on Subject G. V. The open square in the solid areas indicating the average peripheral blood flow marks the lowest level the peripheral blood flow reached as a consequence of smoking.

same brand for all subjects. They were purchased on the open market. The regular and commercially denicotinized cigarettes contained 1.88 per cent and 0.79 per cent of nicotine, respectively.[8] When the water pipe was employed, commercially denicotinized cigarettes were used. The fully denicotinized cigarettes were prepared after the technique of Weatherby.[9] Cigarettes made from cornsilk were of approximately the same size, weight (1 Gm.), and texture as the foregoing types.

RESULTS

The data relating to subject G. V. (Fig. 1) serve to illustrate the effects of smoking the different types of cigarettes. The averages for

all subjects are shown in Fig. 2. The data on all subjects are summarized in Table I.

Effect of Smoking on Peripheral Blood Flow.—The peripheral blood flow decreased in all instances during smoking, regardless of whether the cigarettes were regular ones, commercially denicotinized, fully denicotinized, or made of cornsilk (Fig. 1, Table I). In all instances the

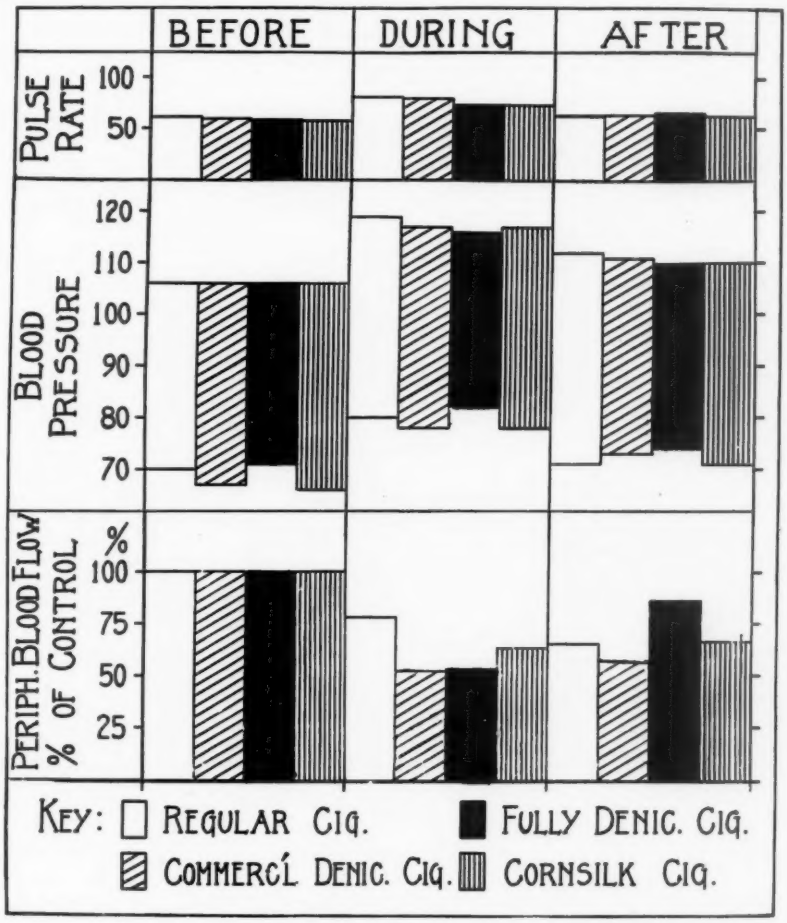

Fig. 2.—Changes in average peripheral blood flow as per cent of the control levels, as well as the average blood pressures and average pulse rates of all subjects before, during, and after smoking regular, commercially denicotinized, and fully denicotinized cigarettes, and cigarettes made from cornsilk.

peripheral blood flow continued to fall in one or more experiments in the first part of the period after the subjects had stopped smoking, but began to rise toward the control levels by the end of thirty minutes after cessation of smoking. In others, after the fall in peripheral blood flow which accompanied smoking, there was a return to control levels as soon as the smoking was discontinued. In the average values given for the periods before, during, and after smoking these trends would not be shown (Table I).

TABLE

DATA RELATING TO THE EFFECT

SUBJECT SEX AGE	CIGARETTE TYPE*	AV. PERIPHERAL BLOOD FLOW C.C./M²/MIN.				AV. BLOOD PRESS. MM.Hg			AV. PULSE RATE PER MIN.		
		BEFORE	DURING	AFTER	LOWEST LEVEL AS RESULT OF SMOKING†	BEFORE	DURING	AFTER	BEFORE	DURING	AFTER
G. V.	Reg. cig.	163	115	105	54	99/65	111/74	103/69	52	62	58
Male	Comm. denic.	134	82	71	2	100/65	112/77	104/66	48	61	48
19	Fully denic.	97	56	54	38	99/62	111/74	106/67	49	61	55
	Water pipe	140	104	97	42	100/65	112/78	107/66	55	63	59
	Cornsilk	119	71	95	0	101/57	112/69	103/63	48	62	52
E. B.	Reg. cig.	119	68	76	0	102/72	117/83	107/73	67	83	71
Male	Comm. denic.	85	50	40	25	107/73	119/81	119/90	61	83	73
24	Fully denic.	49	35	67	0	107/80	117/86	108/78	67	80	69
	Water pipe	97	50	48	0	106/70	122/86	118/78	62	70	67
	Cornsilk	70	24	32	12	100/68	118/86	109/79	68	79	65
F. H.	Reg. cig.	46	19	37	14	94/62	108/76	111/70	59	67	61
Male	Comm. denic.	113	58	129	58	101/68	108/71	105/67	64	70	60
28	Fully denic.	41	8	38	0	113/71	123/86	117/77	59	80	67
	Fully denic.	67	36	63	36	101/69	114/80	107/73	56	72	72
	Cornsilk	72	34	32	0	106/61	118/81	107/71	61	76	61
R. T.	Reg. cig.	60	39	65	39	114/73	126/86	120/79	65	96	72
Male	Comm. denic.	108	44	23	14	108/69	124/84	115/77	59	91	68
28	Cornsilk	86	46	41	9	111/70	119/83	117/76	60	88	63
F. D.	Reg. cig.	61	56	101	56	103/70	118/80	109/71	57	69	57
Male	Comm. denic.	126	73	50	10	103/70	118/80	109/71	58	72	62
22	Cornsilk	116	2	53	2	107/73	118/83	109/73	60	78	62
W. B.	Reg. cig.	77	44	25	0	112/67	119/83	120/79	56	79	65
Male	Comm. denic.	54	4	101	4	103/67	121/85	109/76	61	92	76
30	Cornsilk	72	34	32	0	95/69	114/76	114/66	42	76	66
L. E.	Reg. cig.	87	95	24	0	105/69	123/74	112/60	55	88	63
Male	Comm. denic.	72	68	14	0	112/61	120/72	117/65	43	91	62
31	Cornsilk	49	95	23	3	105/60	119/67	110/65	50	65	49
M. McC.	Reg. cig.	13	21	8	0	101/64	114/69	114/67	60	69	60
Male	Comm. denic.	87	45	99	0	96/58	108/71	102/69	64	73	59
36	Cornsilk	83	39	33	0	96/64	106/67	107/67	57	65	65
R. B.	Reg. cig.	39	10	55	10	105/69	122/81	117/77	60	86	76
Male	Comm. denic.	89	74	43	0	106/70	113/81	109/75	65	78	69
27	Cornsilk	35	44	12	0	100/70	117/79	109/75	63	75	70
W. S.	Reg. cig.	82	85	30	0	121/81	133/94	121/80	71	102	63
Male	Comm. denic.	93	2	34	0	113/73	124/90	115/79	71	91	83
28	Cornsilk	83	70	33	0	112/76	127/90	118/77	55	68	59

*Key: Reg. cig. = regular or standard cigarettes (approx. 1.9 per cent nicotine)

Comm. denic. = commercially denicotinized cigarettes (approx. 0.8 per cent nicotine)

Fully denic. = fully denicotinized cigarettes (contain *no* nicotine; prepared according to technique to be reported by Weatherby)

Water pipe = comm. denic. cigarettes smoked through a water pipe containing cold water (nicotine and some irritating substances removed)

Cornsilk = cigarettes made from cornsilk (no nicotine)

†Lowest observed level of blood flow as the result of smoking (amounts too small to measure are marked zero—0).

I

OF SMOKING ON 10 SUBJECTS

BASAL METABOLIC RATE PER CENT			MAX. TEMP. INCREASE OR DECREASE AS RESULT OF SMOKING ° C.							
			RECTAL		AV. SKIN		HAND		FOOT	
BEFORE	DURING	AFTER	INCREASE	DECREASE	INCREASE	DECREASE	INCREASE	DECREASE	INCREASE	DECREASE
−6	−11	−10	0.05			0.17		1.1		1.2
−14	−14	−12	0.04			0.12		1.0		1.0
−18	−14	−14	0.10			0.21		1.3		2.1
−4	0	+3	0.13			0.06		0.8		1.6
−11	−9	−6	0.08			0.44		1.1		0.6
+2	+5	+7	0.10		0.55			0.4		0.6
0	−2	+4	0.07			0.03		0.4		1.1
−10	−9	−8	0.05		0.25			0.5		0.4
+12	+8	+10	0.18		0.17			1.1		3.0
−4	−7	−7	0.17			0.10		0.1		1.5
−2	0	+4	0.17			0.42		0.6		0.9
+2	+4	+6	0.16			0.67		0.5		0.6
−5	−13	−6	0.08			0.03	0.2			0.7
−4	0	+7	0.15		0.24		0.2			0.6
+5	+2	+2	0.17			0.13		0.2		1.1
−19	−15	−13	0.02			0.08		0.8		3.2
−10	−9	−13	0.07			0.17		1.1		3.8
−18	−16	−14	0.06			0.16		1.2		2.8
−13	−6	0	0.05			1.10		1.3		2.9
−6	−5	−5	0.26			0.35		0.5		2.6
−5	+1	+3	0.13			0.53		1.2		2.5
−3	−6	−7	0.20			0.52		0.5		1.0
+1	+3	+5	0.11			0.31		0.4		0.7
+1	−2	0	0.09			0.12		0.2		1.0
−10	−3	+2		0.08		0.67		0.8		1.6
−13	−4	0	0.29		0.26			1.3		1.4
−10	−9	−5	0.12			0.37		1.1		2.3
−23	−18	−15	0.04			0.22		0.2		1.6
−19	−18	−15	0.06			0.26		1.0		1.5
−19	−16	−11	0.20			0.31		0.6		1.1
+1	0	0	0.05			0.40		0.1		0.2
+3	−3	−7	0.05			0.34		1.4		1.9
−10	+1	−10	0.15			0.23		0.9		1.2
0	−6	−11	0.05			0.46		0.2		2.1
−10	−7	−8	0.13			0.07		1.3		2.6
−12	−11	−15	0.17			0.41		1.2		1.6

Effects of Smoking on Basal Metabolism.—The basal metabolic rate increased slightly, either immediately after smoking or at the conclusion of the measurements, about twice as often as it decreased, regardless of the type of cigarette smoked (Table I). The increases or decreases in oxygen consumption, however, were no greater and were of the same frequency as those among persons of the same age group who lay quietly for the same length of time without smoking.[10]

Effect of Smoking on Blood Pressure and Pulse Rate.—Both the blood pressure and pulse rate rose after smoking every type of cigarette. The rises were of approximately the same magnitude and duration, regardless of the type of cigarette. Similar changes took place when the water pipe was used (Fig. 1, Table I).

Effect of Smoking on Skin Temperature.—A decrease in average skin and hand temperature occurred during and after the smoking of each type of cigarette in all but five instances (Subjects E. B., L. E., and F. H., Table I), and two instances (Subject F. H., Table I), respectively. The foot temperature always decreased. The decrease in the temperature of the hand and foot as the result of smoking was greater than average variations in skin temperature. By comparison, the fall in foot temperature was more marked in most instances than that in hand temperature (Table I, Fig. 1).

Effect of Smoking on Rectal Temperature.—The rectal temperature rose after smoking in all except one instance (Subject L. E.), and to approximately the same extent regardless of the type of cigarette (Fig. 1, Table I).

Effect of Smoking on Electrocardiograms.—Smoking every type of cigarette resulted in an increase in heart rate. The most common change was a decrease in the amplitude of the T waves in one or more leads; this occurred in 71 per cent of the tests. An increase in amplitude occurred in 20 per cent of the tests, and no change in 9 per cent. When the amplitude decreased in several leads it might increase in one lead, or the T wave might become negative, decrease in negativity, or become upright. No correlation was apparent between an increase or decrease in amplitude and the type of cigarette. That is to say, as marked a change was produced by smoking cornsilk, fully denicotinized cigarettes, or commercially denicotinized cigarettes as by smoking regular cigarettes. The maximum change in amplitude was about 1 mm. The greatest change usually accompanied the greatest change in heart rate.

DISCUSSION

The peripheral blood flow decreased as the result of smoking in all instances, regardless of whether the subjects smoked regular, commercially denicotinized, fully denicotinized, or cornsilk cigarettes, or smoked cigarettes through a water pipe (Table I, Fig. 2). It must be emphasized that the subjects were normal persons in the third decade of life,

and were free from arterial disease. The greatest percentage decrease in blood flow took place when the subjects smoked commercially and fully denicotinized cigarettes (Fig. 2). In some instances the peripheral blood flow continued to fall after the subject stopped smoking, but in all it had begun to return to, or had attained, control levels at the end of thirty minutes after smoking (Table I, Fig. 1). The kind of cigarette smoked had no bearing on whether the peripheral blood flow continued to fall or began to return toward control levels, or on how much the peripheral blood flow decreased as the result of smoking (Table I).

Wright and Moffat[3] observed a decrease in the blood flow in the finger tip and toe tip when their subjects smoked cigarettes containing nicotine, but no effect when cigarettes prepared from shredded, ashless filter paper were smoked. We used cornsilk as a control because cigarettes made from it simulated tobacco cigarettes in texture, weight (approximately 1 Gm.), size, and moisture content, and the smoke could be inhaled with ease. Ease of inhalation of the smoke and the basal metabolic state were required in order to have as many factors constant as possible. Ashless filter paper cigarettes prepared according to the technique of Wright and Moffat[3] did not conform to the standards as set forth in the plan of procedure. We prepared and attempted to use a cigarette made of ashless filter paper in order to repeat Wright and Moffat's observations with our method of measuring peripheral blood flow. Because the smoke could not be inhaled without causing violent coughing, data collected on two subjects (L. E. and W. S., Table I) with the use of these cigarettes were not considered sufficiently accurate for comparison, and further tests were not carried out.

Our observations on peripheral blood flow with respect to the smoking of regular cigarettes were similar to the inferences drawn by Maddock and Coller[1] and Wright and Moffat[3] from the fall in skin temperature. On the other hand, when their subjects smoked cigarettes that contained no nicotine, only a negligible fall in the skin temperature of the fingers was observed. Using cubeb for comparative or control cigarettes, as was done by Maddock and Coller,[1] may lead to confusion, for this substance may have some medicinal properties, and is employed in the treatment of asthma.

Our observations are not strictly comparable to those of Maddock and Coller[1] and Wright and Moffat[3] because they measured the temperature of the fingers, which is labile. In the method we employed the average skin temperature is secured by weighting temperatures from several parts of the body.[6] The temperature and blood flow in one part of the body may alter in a different way from another part of the body.

The method we employed in these studies takes account of the peripheral blood flow for the whole body surface in c.c./M^2/Min. The surface area of the hands and feet together represents 12 per cent of the total body surface, according to the estimates of Hardy, DuBois,

and Soderstrom;[11] the finger[1] and the finger tips and toe tips[3] constitute only a very small percentage of these parts. Moreover, the method we have employed not only takes into account the other 88 per cent of the surface area, but also the rectal temperature, which has been given a weighting of 80 per cent of the total body mass by Hardy, DuBois, and Soderstrom.[11]

Mulinos and Shulman[4] have stated that deep breathing alone can account for the greater part of the decrease in blood flow to the hand. In thirteen of sixteen subjects they found that a single deep breath caused complete cessation of blood flow through the capillary tuft of the nail fold. Deep breathing of room air did not bring about this result in any of the subjects studied by Wright.[12] Mulinos and Shulman[4] and Wright,[12] however, did not qualify the depth of the inspiration taken by their subjects. If their subjects took a full inspiration, their inhalations would be exaggerated in comparison with those during *normal* smoking. In the studies now being reported, exaggerated smoking technique was *not* employed. The subjects inhaled, as mentioned earlier, with their normal depth and frequency. This type of inspiration did not induce any significant change in skin temperature. Moyer and Maddock[13] found that when smoking was simulated, only negligible effects were observed in their subjects. We measured the effect of breathing pure oxygen and hot air upon the peripheral blood flow, and observed no decrease in blood flow or rise in blood pressure or pulse rate. Decreases in blood flow as the result of smoking the various types of cigarettes used in this study, therefore, were not attributed to the nicotine content, to the depth of inspiration, or to the inhalation of oxygen or hot air, but to the smoke itself.

As a result of smoking the different types of cigarettes, the basal metabolic rate of the group increased slightly about twice (69 per cent) as often as it decreased (31 per cent) (Table I). Eighty-two per cent of the subjects studied by Hiestand, Ramsey, and Hale[14] showed an increase in basal metabolic rate. Their subjects smoked regular cigarettes only, and were not studied under basal conditions. The results of our studies on subjects in the basal metabolic state showed that, when regular cigarettes were smoked, slight increases occurred in 69 per cent, and decreases in 31 per cent, of the observations (Table I). These data are in close agreement with recent measurements by Goddard and Voss.[15] Their subjects were observed while smoking regular cigarettes under basal conditions. They found an increased metabolic rate in 60 per cent of their subjects and a decreased rate in 35 per cent. These changes do not appear to be significant with respect to the effect of tobacco on the basal metabolic rate, for the increases and decreases in oxygen consumption were no greater than those which occurred in normal persons of the same age, who lay quietly for the same length of time without smoking.[10]

Increases in pulse rate and blood pressure were observed as the result of smoking the various types of cigarettes. These changes were of the same magnitude and duration, regardless of the kind of cigarette (Figs. 1, 2) (Table I). Main[16] found that fully denicotinized cigarettes caused less rise in blood pressure and pulse rate than did regular cigarettes. His results, however, were obtained from a standard exaggerated smoking technique. Maddock and Coller[1] observed no change in blood pressure or pulse rate when their subjects used a water pipe or smoked cubeb, but definite increases in blood pressure and pulse rate occurred when regular cigarettes were smoked. When our subjects used the water pipe, a definite increase in blood pressure and pulse rate was observed (Table I, Fig. 1). The difference between these observations and those of Maddock and Coller[1] may possibly be explained by the choice of method. The use of cubeb, as mentioned earlier, as a control makes evaluation of the results difficult, because it has been smoked by asthmatics to relieve their attacks. If smoke itself brings about peripheral vasoconstriction, with increases in blood pressure and pulse rate, it seems quite possible that these effects may have been nullified by that substance in cubeb which relieves attacks of asthma. Although the subjects of Wright and Moffat[3] smoked cigarettes which contained no nicotine, their report showed no data relating to changes in pulse rate or blood pressure.

There was a decrease in average skin temperature in all except one instance when the subjects smoked regular cigarettes (E. B.), and commercially denicotinized cigarettes (L. E.), but in every instance after cornsilk cigarettes (Table I). Small increases in average skin temperature were observed in two out of four observations, when two of three subjects smoked fully denicotinized cigarettes. Two of the four experiments were done on the same person (F. H., Table I). The first observations on this subject showed a fall in average skin temperature as the result of smoking, the subsequent one, a rise. At the same time, this subject showed small increases in hand temperature and moderate decreases in foot temperature during both experiments. The other subject, who showed an increase in average skin temperature as the result of smoking fully denicotinized cigarettes, also showed an increase when the water pipe was employed. The hand and foot temperatures fell during both experiments on this subject (E. B., Table I).

Not only subjects F. H. and E. B., but each subject in the group showed a varying response to smoking from one experiment to the next. For example, at a time when subject R. B. (Table I) showed the greatest decrease in *average* skin temperature, the least decrease occurred in the temperature of his extremities. Subsequent observations on this subject showed the reverse type of response. Analysis of the data in Table I shows that other subjects responded in a similar manner. These data demonstrate, therefore, that a subject reacted differ-

ently from day to day, and that there was no direct relationship between the average skin temperature and the temperature of the hand or foot (Table I).

Goddard and Voss[15] reported that the body temperature was usually higher after smoking. They did not specify, however, how or where the body temperature was measured. In our experiments, rapid increases in rectal temperature resulted from smoking in all but one instance, in which a fall occurred. This took place when one of the subjects (L. E.) smoked regular cigarettes (Table I). We wish to emphasize the increase in rectal temperature. We think that the sudden rises in rectal temperature are important as an index of peripheral vasoconstriction and decreased peripheral blood flow, for the internal temperature represents about 80 per cent of the total body mass.[11] The sudden increases in rectal temperature indicated increased heat storage. Examination of the data showed that increased heat storage could be accounted for only in part by increased heat production (basal metabolism). It follows, therefore, that the body stored heat because peripheral vasoconstriction decreased the allocation of blood to the surface. The peripheral vasoconstriction and decreased peripheral blood flow were such that 80 per cent of the body mass gained heat rapidly.

The most common change in the electrocardiogram caused by smoking was lowering of the amplitude of the T waves. This change was slight, and usually did not exceed 1 mm. An increase in amplitude, as well as no change, was also recorded. Since these effects were produced by smoking cornsilk, fully denicotinized cigarettes, and commercially denicotinized cigarettes, as well as regular cigarettes which contained nicotine, it is apparent that they cannot be attributed to the nicotine content of smoke. These results are similar, in the main, to those described by Graybiel, Starr, and White.[17] They attributed the changes which they recorded to the nicotine content of tobacco smoke, but our observations make it appear unlikely that nicotine is responsible. The changes are similar to those observed by Hartwell, Burrett, Graybiel, and White[18] after exercise and atropinization, and may be associated with the increase in heart rate and whatever adjustments increase in rate may require in the organism.

The observations now being reported have shown that smoke which contained *no* nicotine had the same effect (decrease in peripheral blood flow, increase in blood pressure and pulse rate) as smoke which contained it. It is apparent that nicotine cannot be responsible for the effects we have observed, and the question naturally arises as to what the cause may be. Willius, in the course of his discussion of a paper on "Tobacco and Coronary Disease," by English, Willius, and Berkson,[19] said, in part: "You will note that we have carefully avoided the use of the term *nicotine*, but said *tobacco smoke*, because we have

reasons to believe that probably more than the chemical agent nicotine plays a part."

Haag,[2] working with animals, demonstrated that the effects of smoke solutions were proportional to their nicotine content. In addition, it has been shown by Maddock and Coller[1] and Haag[2] that nicotine alone, without smoke, may induce changes in the circulation similar to those we have described. The work of Haag indicates that nicotine has a quantitative effect, but the results of Wright and Moffat[3] and Mulinos and Shulman[4] showed no essential difference between the effects of smoking standard cigarettes and cigarettes which contained only 40 per cent as much nicotine. If nicotine had been the responsible factor in our experiments, changes of greater magnitude might have been expected from cigarettes which contained it because of the additive effect of smoke and nicotine, for denicotinized cigarettes brought about similar changes. Such an additive effect was not observed in any instance. Sympathetic stimulation brought about by the irritating effect of smoke upon the respiratory tract, independent of nicotine, may be responsible for the changes we have observed.

The smoking of tobacco has been generally regarded as deleterious in certain peripheral vascular diseases. The data now being presented indicate that smoking any type of cigarette may be harmful, and that smoking denicotinized cigarettes is not a substitute for not smoking.

SUMMARY

The effect of smoking cigarettes on the peripheral blood flow was studied by means of a method with which the average amount of blood allotted to the periphery can be measured in c.c./M²/Min. Peripheral blood flow was measured in ten normal male subjects. Effects on the electrocardiogram, basal metabolic rate, blood pressure, and pulse rate were also recorded. Studies were made before, during, and after the smoking of regular cigarettes, commercially denicotinized cigarettes, and cigarettes made from cornsilk. Observations were made on ten male subjects whose ages ranged from 19 to 36 years. Four observations relating to fully denicotinized cigarettes were made on three of the subjects. Measurements were made also when two of the subjects smoked cigarettes through a water pipe.

1. As a result of smoking, a decrease in peripheral blood flow occurred in every instance, regardless of the type of cigarette smoked. After cessation of smoking, the peripheral blood flow continued to decrease in some cases and began to return toward control levels in others. In all, a return toward normal had begun by the end of thirty minutes after smoking had stopped.

2. An increase in blood pressure and pulse rate of essentially the same magnitude and duration resulted from smoking every type of cigarette.

3. The average skin temperature decreased in all but five experiments. The hand temperature fell in every instance except two. The foot temperature always decreased. The decrease in foot temperature was greater than that in hand temperature on all but two occasions.

4. Rapid rises in rectal temperature occurred in all experiments except one. These rapid rises in rectal temperature were considered an important index to peripheral blood flow.

5. As the result of smoking, small increases in basal metabolic rate were observed about twice as often as small decreases. The change had no relationship to the kind of cigarette, and was of about the same amount and duration as the changes which occur when normal subjects lie in bed for the same length of time without smoking.

6. The changes in the electrocardiogram were slight and probably of no significance.

7. Since these changes occur after smoking cigarettes which do not contain nicotine as well as those which do, they are not to be attributed to nicotine. It is suggested that sympathetic stimulation brought about by the irritating effect of smoke upon the respiratory tract may be responsible for the changes we have observed.

8. It appears that smoking not only regular cigarettes, but also denicotinized cigarettes or cigarettes of any type should be avoided in the presence of peripheral vascular disease.

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THE COURSE OF THE BLOOD PRESSURE BEFORE, DURING, AND AFTER CORONARY OCCLUSION

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AN EARLY fall in blood pressure is one of the cardinal signs of coronary occlusion,[1] and its importance in the differentiation of this disease from angina pectoris was recognized as early as 1915.[2] There has been relatively little systematic study of the course of the blood pressure during the entire attack. Observations on the blood pressure in the years subsequent to the attack have been reported by Palmer[3] and Master, et al.[4, 5] The present report is based on a detailed study of the blood pressure before, during, and after coronary occlusion in a large series of cases.

Particular interest was paid to the following: the influence of hypertension on prognosis during and after the attack; the number of patients who lose their hypertension during the attack and recover it later; the relation of the fall in blood pressure to the height of the blood pressure prior to the attack; the significance of the rapidity and degree of fall in blood pressure and in pulse pressure; the causes of the immediate fall in blood pressure and of the permanent lowering after recovery; the influence of hypertension after the attack on the development of angina pectoris, heart failure, coronary occlusion, and death.

MATERIAL

Blood pressures were recorded frequently after five hundred thirty-eight attacks of acute coronary occlusion. Slightly over half of these were initial attacks and the remainder were second or third attacks (Table I). Four hundred sixteen of the attacks occurred in men and one hundred twenty-two in women (Table II), a ratio of 3.4 to 1, which is usual. Recovery occurred in three hundred eighty-three cases (71 per cent), and two hundred five of these patients were followed for a period of one to seven years (average, three and one-half to four years[4, 5]). In these cases blood pressure readings were taken every three to six months and were correlated with the degree of functional recovery and the presence of angina pectoris, heart failure, and subsequent attacks of occlusion. The latter occurred in fifty-one patients.

RESULTS

Incidence of Hypertension Prior to the Attack.—We employed the following criteria in judging whether hypertension had been present before the attack: (1) a systolic pressure of 150 mm. or more at any time during observation; (2) a diastolic pressure of 96 mm. or more

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prior to the attack; (3) a diastolic pressure of 90 mm. or more during or after the attack; and (4) marked enlargement of the heart without obvious cause. The application of these criteria showed that 69 per cent of the patients had hypertension before the attack (Table I). Eleven per cent had been nonhypertensive and the remaining 20 per cent probably had had normal blood pressure, that is, they were seen only after the onset of the attack, and the blood pressure did not reach a hypertensive level even after recovery. The actual incidence of hypertension was doubtless greater than 69 per cent, for, in many cases, this figure was based on readings obtained only during the attack, when the blood pressure was low. In favor of this view is the fact that the incidence of hypertension in the cases of fatal coronary occlusion was much lower than in those of nonfatal occlusion (Table I). Since previous hypertension does not significantly affect the mortality rate in the attack,[6] one may assume that hypertension was as common when the attack was fatal as when it was not. A low figure was observed among the patients who died because their blood pressure did not return to previous levels. It is probable, therefore, that the incidence of hypertension in our series was at least 70 to 75 per cent.

TABLE I

INCIDENCE OF PREVIOUS HYPERTENSION

538 ATTACKS

ATTACK	NO.	HYPERTENSION	PROBABLY NORMAL B.P.	NORMAL B.P.
Initial				
Nonfatal	207	146 (71%)	53 (25%)	8 (4%)
Fatal	70	34 (49%)	14 (20%)	22 (31%)
Multiple				
Nonfatal	176	136 (77%)	21 (12%)	19 (11%)
Fatal	85	54 (64%)	20 (24%)	11 (12%)
Total	538	370 (69%)	108 (20%)	60 (11%)

TABLE II

INCIDENCE OF PREVIOUS HYPERTENSION BY SEX

538 ATTACKS

SEX	NO.	HYPERTENSION	PROBABLY NORMAL B.P.	NORMAL B.P.
Male	416	267 (64%)	89 (21%)	60 (15%)
Female	122	99 (81%)	17 (14%)	6 (5%)

Hypertension was more frequent with multiple than with initial attacks (Table I) and in women than in men (Table II). Sixty-four per cent of the men and 80 per cent of the women had an elevated blood pressure at one time or another.

The frequency of hypertension increased with age. We have previously shown[6] that the incidence rises from 28 per cent at the age of 25 to 34 years to 80 per cent at 75 years and over. In the present series, twenty-five patients were less than 40 years old, and only nine

of these (36 per cent) had hypertension. Thus the incidence was half of that in the aged. This relatively low frequency of hypertension in the young was observed also by Glendy, Levine, and White.[7]

TABLE III

COURSE OF BLOOD PRESSURE DURING ACUTE ATTACK

205 CASES

	RAPID FALL	GRADUAL FALL
Hypertensive	34.5%	29.5%
Nonhypertensive	22.5%	13.0%
Total	57.0%	42.5%

The Blood Pressure During the Attack.—The blood pressure always fell during the attack. Although the rapidity and degree of fall varied considerably, we have been able to classify the blood pressure course during and after the attack into several types, according to the initial level, the degree and rapidity of fall and return toward the previous level, and the outcome of the attack. Graphs were drawn to illustrate each type; each graph was based on the actual readings in a representative case. The results are summarized in Table III.

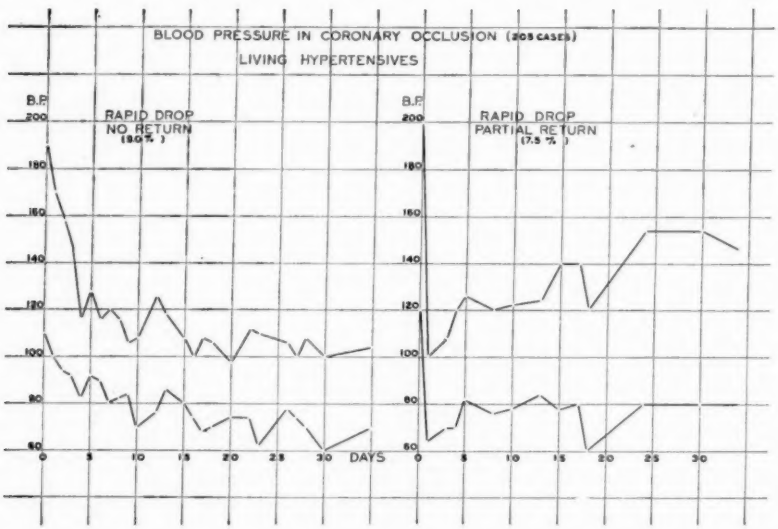

Fig. 1.

Fifty-seven per cent of the patients (Table III) showed a rapid fall, that is, in the first three days the blood pressure fell to a level approaching the lowest pressure during the attack (Figs. 1, 2, 5, 7, 9). In 42.5 per cent the fall was gradual, reaching a low level in one to three weeks (Figs. 4, 6, 8, 9). Occasionally a week or more elapsed before a significant fall became evident; this was observed also by Allen.[8] In the majority of cases the lowest pressure was reached be-

tween the twelfth and twentieth day (Figs. 2, 3, 4). The rapidity of the fall in blood pressure was influenced to some extent by the height of the pressure preceding the onset of the attack. A greater percentage of nonhypertensive patients showed a rapid fall than did those

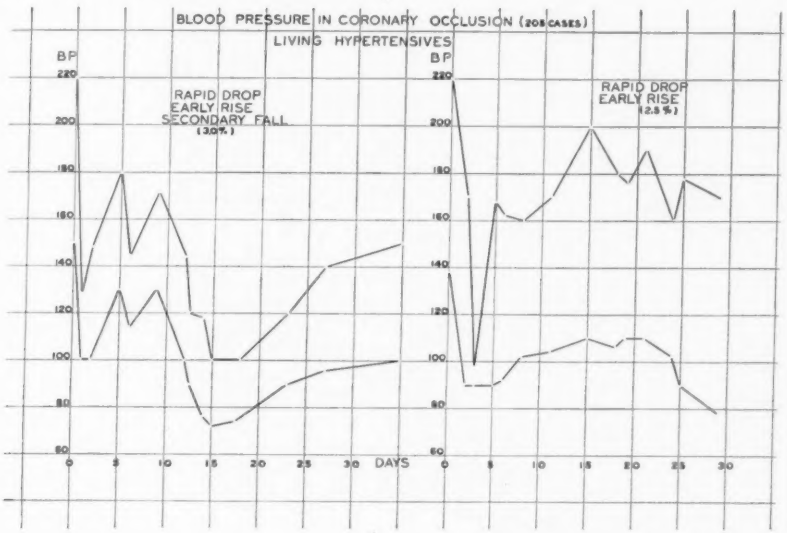

Fig. 2.

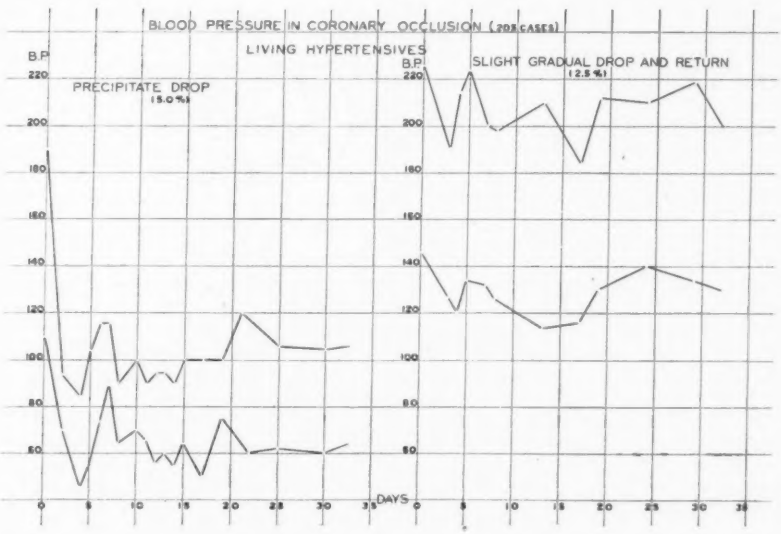

Fig. 3.

with hypertension. The most rapid fall seemed to occur in nonhypertensive cases in which the attack was fatal (Fig. 9). In the hypertensive group the incidence of a rapid fall was the same in the fatal and nonfatal cases. It appears from a study of the graphs that, in general,

TABLE IV

INCIDENCE OF SYSTOLIC BLOOD PRESSURE BELOW 100 MM. DURING ACUTE ATTACK

538 CASES

	HYPERTENSIVE CASES (370)		NONHYPERTENSIVE CASES (168)		TOTAL 538
	NONFATAL	FATAL	NONFATAL	FATAL	
First Day	3%	10%	14%	31%	9%
Lowest	24%	31%	48%	50%	34%
Discharge	4%	21%	19%	28%	13%

the trend of the blood pressure curves was similar in the hypertensive and nonhypertensive groups; of course, the absolute fall in pressure was greater in the hypertensive group.

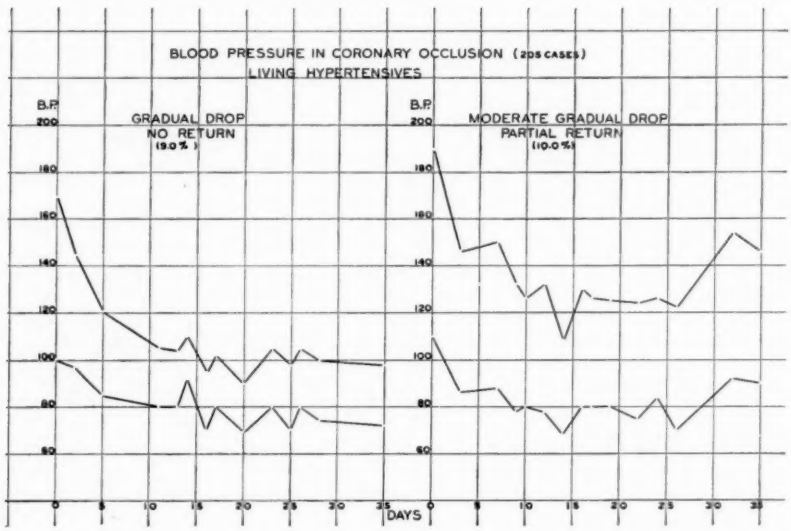

Fig. 4.

Although one is likely to associate coronary occlusion with a precipitate fall in pressure, that is, to less than 100 mm. during the first day, this occurred in only 9 per cent of our cases (Figs. 3, 7, 9). Frequently the fall was not great in the first twenty-four hours (Table IV). In hypertensive patients the systolic pressure rarely fell below 90 mm., and, in only 26 per cent, did it go below 100 mm. during the attack; these figures were practically never reached on the first day of the attack (Table IV). Of the nonhypertensive patients, on the other hand, the systolic blood pressure fell below 90 mm. at some time during the attack in 38 per cent, and below 100 mm. in almost half; the latter level was present on the first day in 22 per cent (Tables IV and VI). As might be expected, the frequency of systolic blood pressures below 100 mm. was greater when the attack was fatal; this was true in both the nonhypertensive and hypertensive groups (Table IV).

The more precipitate and marked the fall, the more severe the attack and the greater the degree of shock.[8] A systolic pressure below 80 mm. was usually of grave significance.[1, 9] However, the fall in blood pressure at the onset of the attack was not always of paramount prognostic

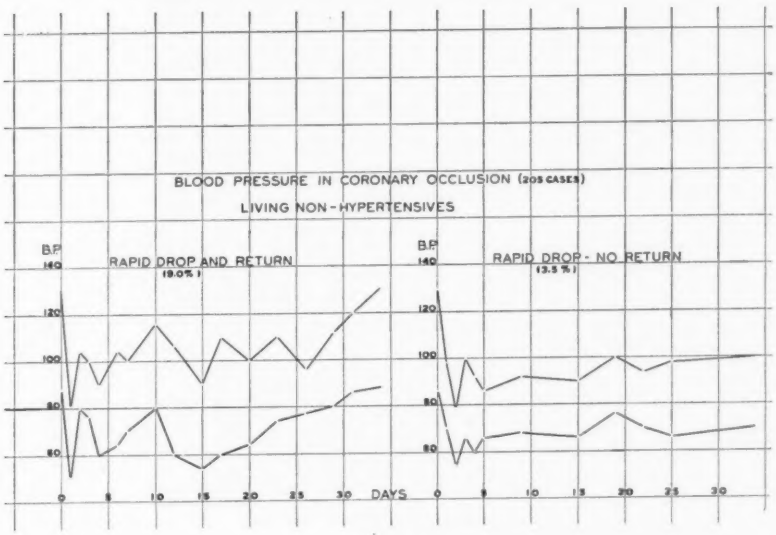

Fig. 5.

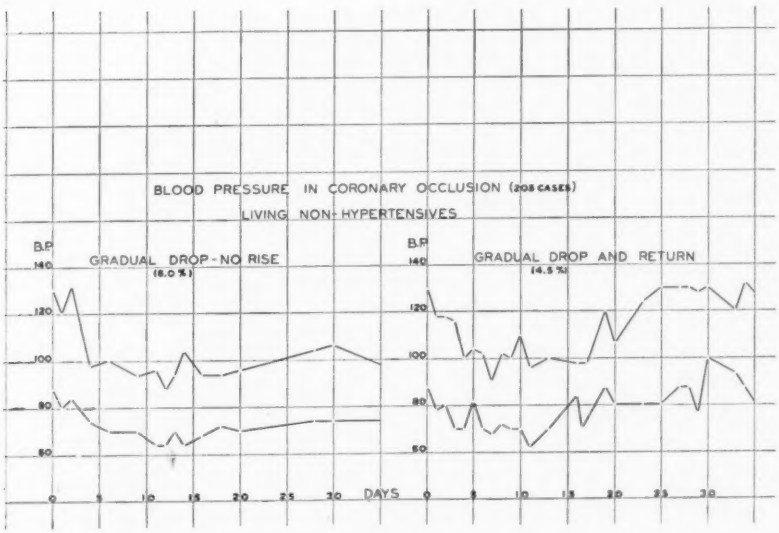

Fig. 6.

significance, for, occasionally, a patient recovered in spite of an initial systolic blood pressure of 70 or 80 mm.[10] On the other hand, two patients died early in the attack when their systolic blood pressure was still over 200 mm.

The actual fall in pressure depended largely upon the initial level (Tables V and VI). Thus, in 20 per cent of the patients who survived and had an initial systolic pressure of 200 mm. or more, the pressure did not fall below 150 mm., and in only 11 per cent did it fall below 100 mm. (Figs. 1 and 2). In this group the pressure not infrequently fell only slightly during the first four or five days (Fig. 3). On the other hand, in the group with a previous blood pressure of 150 to 190 mm., a fall below 150 mm. occurred in all but 3 per cent, and below 100 mm. in 30 per cent (Fig. 4).

TABLE V

RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO LOWEST PRESSURE DURING ACUTE ATTACK

198 CASES OF HYPERTENSION

PREVIOUS B.P.	NO.	B.P. DURING ATTACK		
		150-	100-150	100
200-	45	9 (20%)	31 (69%)	5 (11%)
170-199	76	5 (7%)	47 (62%)	24 (31%)
150-169	77	3 (4%)	50 (65%)	24 (31%)
Total	198	17 (8%)	128 (65%)	53 (27%)

TABLE VI

RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO LOWEST PRESSURE DURING ACUTE ATTACK

86 PATIENTS WITHOUT HYPERTENSION

PREVIOUS B.P.	NO.	B.P. DURING ATTACK			
		110-119	100-109	90-99	90
130-149	17	3	5	6	3
110-129	61	5	11	20	25
100-109	8	0	1	2	5
Total	86	8 (9%)	17 (20%)	28 (33%)	33 (38%)
Nonfatal	38	4	9	17	8 (21%)
Fatal	48	4	8	11	25 (52%)

Occasionally the onset of coronary occlusion with severe pain was associated with a transitory rise in blood pressure which sometimes reached 200 mm., systolic. This was noted also by Weiss[11] and Scherf and Boyd.[12]

Although the blood pressure usually fell progressively, and reached its lowest level between the twelfth and twentieth days (Fig. 1), this was not always the case. In a small group of patients with hypertension, totaling 3 per cent of the series (Fig. 2), the fall in blood pressure was interrupted by a transitory rise early in the attack, followed by a secondary fall in the second week. In another small group (2.5 per cent) of hypertensive patients (Fig. 2), the early rise which followed the initial drop was permanent, and the blood pressure remained elevated throughout the patient's hospital stay, although pre-attack levels were not attained. In cases in which the attack was fatal the blood pressure generally persisted at its lowest levels until death.

However, in a small group of hypertensive patients who survived for several days or weeks, the initial rapid fall was followed by a slight rise before death (Fig. 7). Similarly, in a small group of nonhypertensive patients the blood pressure actually returned to normal before death (Fig. 9).

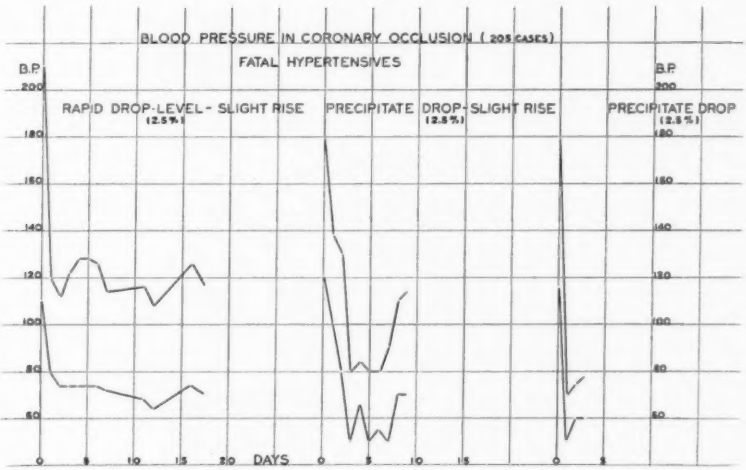

Fig. 7.

TABLE VII

RELATION OF SMALLEST PULSE PRESSURE TO MORTALITY RATE DURING ACUTE ATTACK

538 CASES

PULSE PRESSURE	HYPERTENSIVES		NONHYPERTENSIVES	
	NO.	MORTALITY	NO.	MORTALITY
70-79	2	0	0	0
50-69	55	21%	2	0
30-49	145	20%	44	18%
20-29	131	23%	69	33%
10-19	36	32%	52	73%
10	1	1 case	1	0
	370	24%	168	40%

The Pulse Pressure During the Attack.—In general, the diastolic pressure followed the same trend as the systolic, but the fall in the former was usually less precipitate and less marked than that in the systolic. This resulted in a decrease in the pulse pressure, often to as low as 10 to 20 mm. (Fig. 2). In the hypertensive group the pulse pressure usually ranged between 20 and 50 mm. (Table VII). In the majority of the nonhypertensive patients it fell between 10 and 40 mm.

In a previous study[13] it was found that the decrease in pulse pressure was not significant from the point of view of the severity and prognosis of the attack, unless it fell below 20 mm. Coombs[14] regarded a fall to 25 mm. as serious. Our present observations bear out these conclusions. Table VII shows that the mortality rate rose significantly

when the pulse pressure was less than 20 mm. In such cases there is generally a severe degree of shock and heart failure. However, it is interesting that one patient with a pulse pressure of less than 10 mm. recovered.

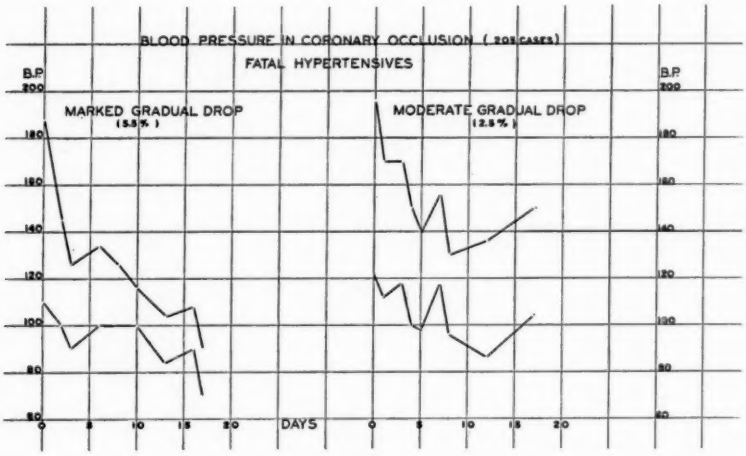

Fig. 8.

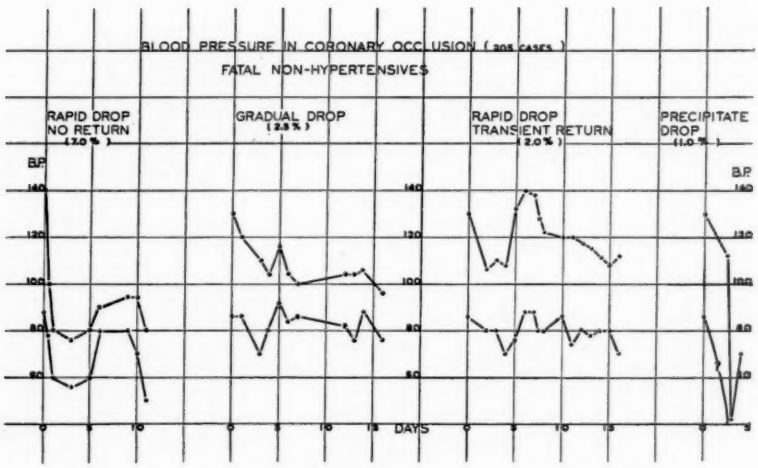

Fig. 9.

Blood Pressure on Discharge.—The blood pressure often persisted at a low level throughout the hospital stay in both hypertensive (Figs. 1, 3, 4) and nonhypertensive patients (Figs. 5, 6); this was true of almost one-third of the patients who survived. In one-third of the entire series there was a gradual return of the blood pressure toward initial levels (Figs. 1, 3, 4, 5, 6). This is shown also by a study of the blood pressures of the patients who survived the attack at the time of their discharge from the hospital (Tables IV, VIII, IX). In the hyper-

tensive group (Table VIII) the blood pressure on discharge had returned to 150 mm. or more in 28 per cent of the cases, and remained below 100 mm. in only 4 per cent (Table IV). The blood pressure generally did not attain the high levels prior to the attack; for example, if the initial pressure had been 170 to 199, the discharge blood pressure was 150 to 169 (Table VIII). It is noteworthy, however, that in two cases the blood pressure on discharge had actually risen to 200 mm. or more.

TABLE VIII

RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO PRESSURE AT TIME OF DISCHARGE

160 CASES OF HYPERTENSION

PREVIOUS B.P.	NO.	BLOOD PRESSURE ON DISCHARGE					
		200-	170-199	150-169	120-149	100-119	<100
200+	34	2	8	9	10	6	0
170-199	14	0	1	3	5	4	1
150-169	18	0	0	1	12	5	0
Hypertension of unknown level	94	0	7	14	42	28	2
Total	160	2	16	27	69	43	3
		45 (28%)			115 (72%)		

TABLE IX

RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO PRESSURE ON DISCHARGE

37 PATIENTS WITHOUT HYPERTENSION

PREVIOUS B.P.	NO.	130-149	BLOOD PRESSURE ON DISCHARGE		
			110-129	100-109	90-99
130-149	8	1	5	2	0
110-129	27	0	13	10	4
100-109	2	0	0	1	1
Total	37	1	18	13	5

As was to be expected, the blood pressure often persisted at lower levels in the nonhypertensive group than in the hypertensive group (Table IX). Thus, in almost one-fifth of the cases the systolic pressure at discharge remained below 100 mm. (Table IV).

Follow-up Study of the Blood Pressure.—In a follow-up study of two hundred twelve cases, Palmer[3] observed that more than half of the patients had developed hypertension within one year after the attack. The number with hypertension then increased year by year until the incidence of hypertension reached 72 per cent, which was the same as before the attack. In our series the number of patients who regained their hypertension after the attack was smaller than in Palmer's series.

A study of Figs. 10 and 11, which show the blood pressure readings one month to seven years after the onset of the attack, reveals that the blood pressure failed to return to previous levels in half of the nonhypertensive and one-third of the hypertensive patients. In another third of the hypertensive group the blood pressure rose to a mild

hypertensive level, usually during the first year after the attack. In the remaining third a rapid rise occurred soon after discharge from the hospital, so that, by the end of the year, the blood pressure had attained the high levels which existed prior to the attack. Although

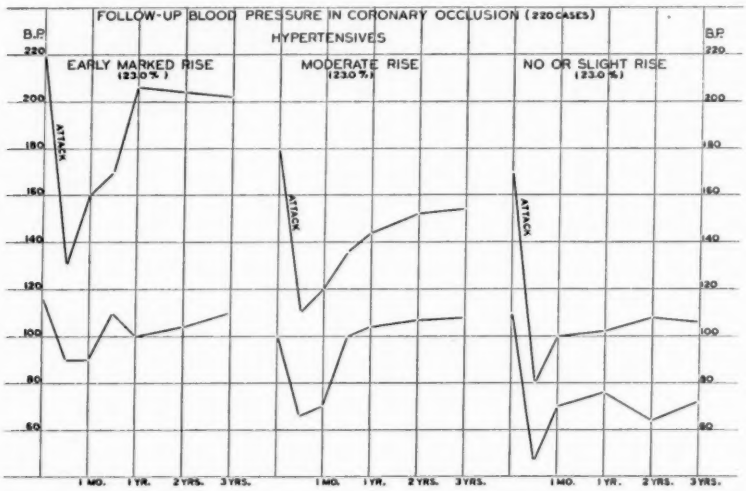

Fig. 10.

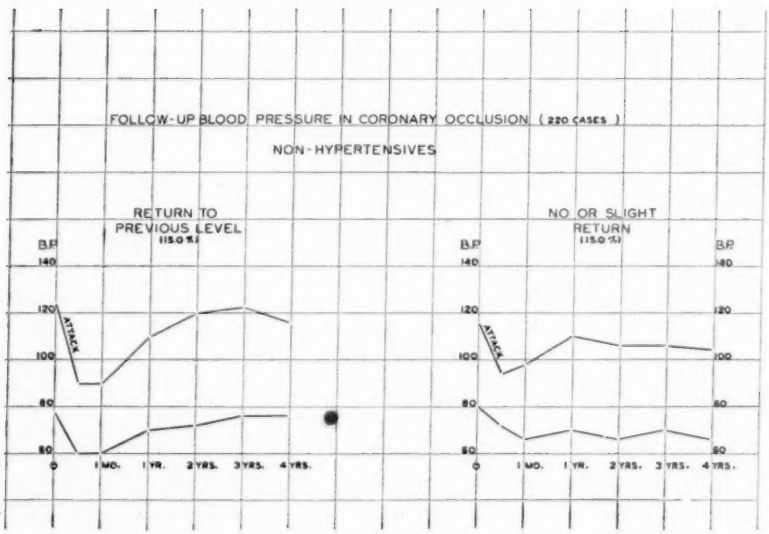

Fig. 11.

this usually occurred within one year after discharge, occasionally the rate of return was slower, so that high levels were reached only in the second or third years. A similar trend was observed in half of the nonhypertensive group.

A summary of these follow-up studies of blood pressure in the hypertensive patients is presented in Table X, in which a comparison is made with previously existing blood pressures. It is seen that the systolic pressure returned to 150 mm. or more in almost two-thirds of the cases. It has already been stated that, in half of these, this level had been reached by the time the patient was discharged from the hospital. In the remaining cases hypertension generally returned during the first or second year. In half the cases in which hypertension returned the blood pressure eventually became approximately the same as before the attack.

TABLE X

RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO FOLLOW-UP PRESSURE
164 CASES OF HYPERTENSION

PREVIOUS B.P.	NO.	FOLLOW-UP BLOOD PRESSURE				
		200	170-199	150-169	120-149	100-119
200+	8	4	3	0	1	
170-199	14	1	5	4	3	1
150-169	14	0	0	8	5	1
Hypertension of unknown level	128	18	28	32	36	14
	164	23	36	44	45	16
		103 (64%)			61 (36%)	

It is evident from these observations that one-third of our hypertensive patients permanently lost their hypertension after acute coronary occlusion. However, the systolic pressure rarely remained at very low levels, and never below 100 mm.

Relation of Late Blood Pressure Levels to Prognosis.—In the past, conflicting views have been expressed concerning the prognostic importance of the height of the blood pressure after recovery from the acute attack. In earlier studies[15, 16] the belief was expressed that another coronary occlusion occurred with greater frequency in patients who regained their hypertension after recovery from the first attack than in those whose blood pressure remained normal. Furthermore, Levine[1] observed that angina pectoris was less frequent and less severe when the pressure did not rise again. On the other hand, Allen[8] stated that the sooner the pressure returned to previous levels the better the prognosis, and that recovery was usually delayed until previous levels were reached. He believed that when the blood pressure fell from 200, systolic, to 100 or 120, and remained there, the prognosis was guarded until a rise in pressure occurred. Similarly, Palmer[18] stated that the prognosis was better in the hypertensive group; low blood pressure did not seem to protect against another attack. Gross and Engelberg[19] disagreed with these views because they observed no effect of hypertension on duration of life or frequency of heart failure following the attack.

The follow-up observations in our series also show that the height of the blood pressure after the attack did not materially influence the

incidence or severity of angina pectoris or the frequency of subsequent attacks of coronary occlusion or of heart failure (Table XI). However, with regard to each of these factors, the patients who never had had hypertension fared somewhat better than those who were hypertensive either before or after the attack. Thus, it seems that when a patient has hypertension prior to the attack the height of the blood pressure after recovery has no prognostic significance. However, the degree of recovery was generally more complete, and the frequency and severity of heart failure less, among patients who had never had hypertension. This is probably attributable to the lower incidence of cardiac enlargement.

TABLE XI

RELATION OF FOLLOW-UP BLOOD PRESSURE TO SUBSEQUENT ANGINA PECTORIS, HEART FAILURE, CORONARY OCCLUSION, AND DEATH

FOLLOW-UP B.P.	NO.	ANGINA PECTORIS	HEART FAILURE	CORONARY OCCLUSION	DEATH
Hypertensive	140	102 (73%)	37 (26%)	33 (24%)	23 (16%)
Normal					
Previously Hypertensive	25	18 (72%)	5 (20%)	9 (36%)	6 (24%)
Never Hypertensive	56	37 (66%)	11 (20%)	9 (16%)	7 (13%)

DISCUSSION

The incidence of hypertension previous to the attack in our series was probably over 70 per cent, a figure which agrees with that of Palmer,[3] namely, 73 per cent. These figures are higher than those usually reported; a survey of the literature[6, 17] reveals an incidence as low as 30 per cent. One explanation for this discrepancy is that a number of authors have used levels higher than ours as criteria of hypertension; some have accepted only 160/100 mm., whereas others have required 110 diastolic. We believe that our figure, 150/96, is accurate. Another reason for our high figure lies in the fact that many of our patients were followed for a considerable period after the attack, during which time the blood pressure frequently returned to a high level. Confirming this view is the point that, in a series previously reported by us,[6] in which the blood pressure was considered during the attack only, the incidence of hypertension was 62.4 per cent. It is probable that the actual incidence in our present series was even higher than our figures indicate, for one-third of the hypertensives never regained their high blood pressure.

The incidence of hypertension in persons over 45 years of age in the general population is not known, although it probably is greater than is commonly thought; we have estimated that it is not more than 50 per cent.[20] This is lower than that in our series, so that it may be concluded that hypertension predisposes to coronary sclerosis, and, therefore, indirectly to coronary occlusion, which occurs in the natural course of coronary sclerosis. However, there is no reason to assume

a direct connection between hypertension and coronary occlusion, as some authors have done.[21, 22] They theorize that hypertension, particularly a sudden rise in blood pressure, may produce the intimal hemorrhage which has been shown to be the most common cause of onset of occlusion.[23] We have already pointed out that there is no experimental evidence for this view, and, in addition, we have presented clinical data in a large series of cases to show that coronary occlusion occurs irrespective of external factors, including changes in blood pressure.[24] A recent report confirms this view.[25] Our pathologic studies also demonstrated that intimal hemorrhages were at least as common among persons with coronary sclerosis without hypertension as among those with it. Intimal hemorrhage in a coronary artery depends merely on the presence of sclerosis; since hypertension is the commonest cause of sclerosis, coronary occlusion is very frequently associated with hypertension. This is particularly true of women, who rarely have coronary sclerosis unassociated with hypertension or diabetes.

Although hypertension plays an indirect role in the pathogenesis of coronary occlusion, it does not affect the course of the disease during or after the attack.[10, 13] The mortality rate at the time of the attack was the same in the hypertensive and nonhypertensive groups. This may be explained partly by the fact that, although cardiac enlargement and failure are more common in hypertension, the blood pressure rarely falls below 100 mm. in this group, whereas a blood pressure under 100 mm. is common in the nonhypertensive group. A systolic blood pressure below 80 mm., and particularly below 70, is usually of grave prognostic significance,[9] yet recovery may take place in spite of such a blood pressure at the onset of the attack. When the blood pressure falls below 80 mm., shock is almost always present. However, it was absent in three cases with such hypotension, in spite of the fact that the previous systolic blood pressure had been over 170 in two cases.

Except for the cases in which the systolic pressure falls below 80 mm., the course of the blood pressure during and after the attack is of no definite prognostic significance. Although in general the fall in blood pressure is greater and more rapid when the disease is severe or fatal, mild attacks may be accompanied by a similar fall in blood pressure, and the latter may not fall dramatically with more severe attacks. It is difficult to predict the course of the blood pressure in individual cases. It is apparent, from the number of graphs presented by us, that in many cases the blood pressure trend in coronary occlusion does not conform to one of the main types. In evaluating the blood pressure, therefore, the clinical course of the patient must be carefully considered.

The mechanism of the initial fall in blood pressure in coronary occlusion remains a moot question. It has usually been attributed to peripheral circulatory failure[9] which is produced reflexly from the

heart and results in pooling of blood in the abdominal organs, with diminution of the venous return to the heart and secondary reduction of the cardiac output. Recently another explanation has been introduced, namely, "cardiac shock."[26, 27] According to this view there is a primary diminution of cardiac output. Whether or not this factor operates immediately after the onset of the attack, it certainly accounts for continued hypotension after the first few days. Its effect usually lasts about two weeks, by which time the cardiac output returns to normal.[28] Thereafter the blood pressure begins to rise toward the level which existed prior to the attack. However, we have shown that one-third of the hypertensives never regain a hypertensive level. The explanation of this is not clear, for the cardiac output is normal and the course of these patients may be as satisfactory as that of patients who regain their hypertension. It is probable that coronary occlusion permanently reduces the peripheral resistance in some cases and not in others.

SUMMARY

The course of the blood pressure before, during, and after the attack has been analyzed in five hundred thirty-eight cases of coronary occlusion.

The incidence of hypertension increased with age.

The blood pressure fell to some extent in every case, although in a few cases the fall was slight. A transitory rise in pressure occurred infrequently at the onset of the attack.

A rapid fall was somewhat more common than a gradual one. Occasionally the fall did not occur until after a week. The lowest pressure was usually reached between the twelfth and twentieth days. In some cases the initial fall was soon followed by a temporary or permanent rise in pressure.

The trend of the blood pressure was similar in the hypertensive and nonhypertensive groups, although a rapid fall was more common among the nonhypertensive patients who died.

The systolic blood pressure rarely fell below 90 mm. in the hypertensive group, but this was common in the nonhypertensive group. When the pressure fell below 80 the patient usually died.

In almost one-fifth of patients with a previous pressure of 200 mm. or more the pressure did not fall below 150 mm.

Two-thirds of the hypertensive patients regained a hypertensive level; in half of these this took place before discharge from the hospital, and, in the remaining half, usually within one or two years.

The height of the blood pressure after the attack did not significantly influence the future course of the patient with respect to subsequent angina pectoris, heart failure, coronary occlusion, or death.

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THE DURATION OF VENTRICULAR SYSTOLE AS MEASURED BY THE Q-T INTERVAL* OF THE ELECTROCARDIOGRAM, WITH ESPECIAL REFERENCE TO CARDIAC ENLARGEMENT WITH AND WITHOUT CONGESTIVE FAILURE

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VARIOUS factors which may influence the duration of the Q-T interval of the electrocardiogram, aside from heart rate, the blood calcium level, and digitalis have received the attention of few workers. One of the most important clinical conditions, namely, cardiac enlargement, has particularly attracted our attention as needing evaluation in this respect.

Although digitalis somewhat shortens the Q-T interval,[1-4] which has been reported as prolonged in heart failure,[7] and a low blood calcium level is associated with considerable prolongation, the Q-T interval varies with the cycle length much more than with any other factor. It is shorter when the heart is rapid and longer when the heart is slow. Fridericia[8] expressed the relationship in the formula: $Q\text{-}T = K \sqrt[3]{C}$, in which C is the cycle length in seconds and K is a constant which he found to be 8.22. Bazett[9] employed a square root equation in another formula: $Q\text{-}T = K \sqrt{C}$, or $K = Q\text{-}T \div \sqrt{C}$. It can be seen from the formula that an increase in the Q-T interval, relative to the cycle length, will result in a smaller value for K. Bazett found that K is normally 0.37 for men and 0.4 for women. White and Mudd[10] constructed a scatter diagram relating to the Q-T interval of normal persons, and found that their results agreed closely with the published data of other workers. These various investigators studied the effect of a wide variety of conditions on the duration of the Q-T interval, but there has been a difference of opinion regarding what constitutes a deviation from normal limits. Adams[11] used a straight-line formula for calculating the predicted Q-T interval:

Male: Q-T = 0.1536, R-R 0.2462
Female: Q-T = 0.1259, R-R 0.2789

More recently, Ashman[12] measured the Q-T intervals of the electrocardiograms of one thousand normal men and women and proposed the logarithmic formula: $Q\text{-}T = K \log [10(C + k)]$. C is cycle length in seconds and k is 0.07. According to this formula, K is 0.377 for men and 0.387 for women. Ashman gave the upper normal limits of K as 0.41 for men and 0.42 for women.

*The Q-T interval is the interval from the beginning of the Q wave to the end of the T wave.

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In 1938, White, Jenks, and Benedict[13] measured the Q-T intervals of the electrocardiograms of a number of circus elephants and found that they were prolonged out of proportion to the heart rates, as compared to the normal human Q-T interval. It was thought that the explanation for this might be found in the immense size of the elephant's heart, with its longer pathways of impulse conduction and its greater bulk of contracting muscle.

This hypothesis suggested that it would be worth while to study the influence of pronounced cardiac enlargement on the duration of the Q-T interval, particularly because such cardiac enlargement in human beings is of serious prognostic importance.

MATERIAL AND METHOD

Two groups of cases were studied. The first group consisted of eleven cases of well-marked cardiac enlargement, with no evidence of congestive heart failure or other complication. The second group of fifteen patients, in addition to cardiac enlargement, also had various degrees of congestive heart failure. The first group was taken from ambulatory patients who presented themselves for routine examination. An attempt was made to select cases of cardiac conditions which produce enlargement affecting primarily one cardiac chamber. In the second group, electrocardiograms were taken soon after admission to hospital. The patients had received no digitalis for at least one month prior to entry. Digitalization was carried out according to the usual routine, and completed in from three days to one week. A second electrocardiogram was taken at the time when the patients had recovered from congestive failure, i.e., from five days to eleven months after the first electrocardiogram.

Only good records with clearly defined QRS waves with well marked T-wave end points were measured. Cases of auricular fibrillation and bundle branch block were excluded. The duration of the Q-T interval of three successive heart cycles was measured in each case, and the results averaged. The cardiac cycle was ascertained by measurements of the Q-Q interval. The Lucas comparator was used for all the measurements; it gives results in ten thousandths of a second, with correct readings to one or two thousandths of a second. The relatively small number of cases studied by us is accounted for by the facts (1) that the great majority of patients with congestive heart failure who came into the hospital had been taking some form of digitalis, (2) that suitable electrocardiograms were not always obtained both during congestive heart failure and after the failure had completely cleared, and (3) that many of the records naturally failed to show sharp end points.

RESULTS AND DISCUSSION

Of the patients with well-marked cardiac enlargement without failure (Table I), six were men and five were women. The average for K, calculated according to Bazett's formula, $K = Q\text{-}T \div \sqrt{C}$, was 0.426 (0.421 for the men and 0.431 for the women). Compared with the values given for normal persons by Cheer and Li,[14] which are 0.374 for men and 0.388 for women, these figures represented an appreciable increase above the normal. However, if the figures of Shipley and Hallaran[15] are used, namely, 0.397 for males and 0.415 for females, the departure from normal is not quite so marked. Calculated according to Ashman's formula,[12] $Q\text{-}T = K \log [10(C + k)]$, the average K in our

cases was 0.405 (0.403 for the men and 0.408 for the women). This again represents an appreciable increase over the values for normal subjects, which are 0.377 for men and 0.387 for women. It is interesting to compare our figures with those of Ashman, who, in a series of cases of various types of heart disease, found that the average K was 0.405 for men and 0.410 for women.

TABLE I

THE Q-T INTERVAL IN CARDIAC ENLARGEMENT

NO.	SEX	AGE	DIAGNOSIS	X-RAY	Q-Q INTERVAL (SEC.)	Q-T INTERVAL (SEC.)	CONSTANT K (BAZETT)*	CONSTANT K (ASHMAN)†
1	F.	62	Hypertensive	Considerably enlarged heart	0.5805	0.3583	0.470	0.441
2	F.	61	Hypertensive	Enlarged left ventricle	0.8170	0.3586	0.396	0.378
3	M.	71	Hypertensive	Moderately enlarged heart	0.8684	0.4220	0.452	0.434
4	M.	48	Hypertensive and coronary	Enlarged heart	0.8490	0.3809	0.415	0.396
5	F.	26	Rheumatic, aortic stenosis and regurgitation	Considerably enlarged heart	0.6005	0.3092	0.398	0.374
6	M.	70	Hypertensive and coronary; aortic stenosis	Big heart	1.2367	0.4365	0.393	0.376
7	F.	70	Hypertensive and coronary; aortic stenosis and regurgitation	Big heart	0.7470	0.3924	0.453	0.431
8	M.	42	Congenitally bicuspid aortic valve, with scarring	Considerably enlarged heart	0.7461	0.3717	0.430	0.408
9	F.	32	Rheumatic, mitral stenosis	Enlarged, round heart	0.5640	0.3349	0.440	0.418
10	M.	41	Rheumatic, mitral stenosis and regurgitation	Enlarged heart	0.8040	0.3837	0.427	0.407
11	M.	12	Auricular septal defect	Prominent pulm. conus, wide across auricles	0.9128	0.3918	0.410	0.394

*$K = Q\text{-}T \div \sqrt{C}$.
†$K = Q\text{-}T \div \log [10(C + k)]$.

Although the average value for K in our present series shows that the Q-T interval is definitely prolonged in relation to the heart rate, it must be pointed out that in only six of the eleven cases, or 55 per cent, were the values of K at or beyond the upper limits of normal. It made no appreciable difference whether the enlargement affected the right or

TABLE II

Q-T INTERVAL WITH AND WITHOUT FAILURE

NO.	SEX	AGE	DIAGNOSIS	DURATION OF FAILURE	X-RAY	INTERVAL BETWEEN ELECTROCARDIOGRAMS	CONDITION	Q-Q INTERVAL (SEC.)	Q-T INTERVAL (SEC.)	CONSTANT K (BAZETT)*	CONSTANT K (ASHMAN)†
1	F.	48	Coronary	5 months	Heart enlarged especially left	14 days	In failure	0.7228	0.4246	0.498	0.472
							Out of failure	1.040	0.3487	0.341	0.334
2	F.	56	Coronary	3 months	Enlarged left ventricle	15 days	In failure	0.7757	0.4278	0.485	0.462
							Out of failure	0.8273	0.4116	0.452	0.432
3	M.	45	Coronary	1 year	Enlargement all directions	7 days	In failure	0.6179	0.3577	0.455	0.427
							Out of failure	0.8087	0.3834	0.426	0.406
4	M.	54	Coronary	3 months	Heart enlarged especially left	20 days	In failure	0.6837	0.3307	0.400	0.377
							Out of failure	1.0224	0.3506	0.348	0.338
5	M.	57	Coronary	4 weeks	Heart enlarged especially left	23 days	In failure	0.7452	0.3491	0.404	0.383
							Out of failure	0.7045	0.3298	0.392	0.371
6	M.	52	Coronary	3 weeks	Heart enlarged	14 days	In failure	0.7255	0.3653	0.426	0.406
							Out of failure	0.8689	0.3546	0.382	0.365
7	M.	56	Hypertensive and coronary	3 months	Heart enlarged both sides	11 months	In failure	0.7795	0.3713	0.421	0.400
							Out of failure	0.8541	0.3357	0.363	0.348
8	F.	53	Hypertensive and coronary	3 weeks	Heart diffusely enlarged	3 months	In failure	0.9295	0.4120	0.428	0.412
							Out of failure	0.7701	0.3697	0.422	0.400
9	M.	56	Hypertensive and coronary	6 months	Heart enlarged, especially left	6 days	In failure	0.7147	0.3897	0.462	0.436
							Out of failure	0.8417	0.3681	0.401	0.384
10	M.	54	Hypertensive and coronary	6 weeks	Hypertrophy left ventricle	23 days	In failure	0.5992	0.3778	0.488	0.458
							Out of failure	0.6911	0.3269	0.392	0.372
11	M.	57	Hypertensive	10 days	Heart greatly enlarged, especially left	27 days	In failure	1.1101	0.4242	0.402	0.394
							Out of failure	0.9656	0.3822	0.389	0.376
12	M.	55	Hypertensive	1 year	Heart enlarged especially left	17 days	In failure	0.7819	0.3805	0.430	0.409
							Out of failure	0.7970	0.3590	0.402	0.382
13	M.	49	Hypertensive	5 months	Enlarged, both sides	29 days	In failure	0.5748	0.3209	0.425	0.396
							Out of failure	0.5960	0.3297	0.426	0.400
14	M.	47	Hypertensive	3 weeks	Enlarged, both sides	5 days	In failure	0.6872	0.3500	0.422	0.398
							Out of failure	0.7559	0.3770	0.433	0.411
15	M.	37	Hypertensive	2 months	Heart enlarged especially left	6 days	In failure	0.7463	0.3601	0.418	0.395
							Out of failure	0.8240	0.3424	0.377	0.360

*$K = Q\text{-}T \div \sqrt{C}$. †$K = Q\text{-}T \div \log [10(C+k)]$.

left ventricle. When Bazett's formula was used, the average K for the eight cases of left-sided enlargement was 0.426, and, for the three cases of right-sided enlargement, it was also 0.426.

In the second group (Table II), the Q-T interval of the patients with failure showed still more prolongation beyond normal limits. The average K in these cases was 0.438, according to Bazett's formula (0.430 for the men and 0.471 for the women). Cheer and Dieuaide,[7] using the same formula, found that the value of K was 0.432 for men, and 0.433 for women, with cardiac failure. Their series included relatively few cases of coronary heart disease. Our results in six cases of coronary heart disease and four cases of hypertensive and coronary heart disease confirm their observations. When Ashman's logarithmic formula was used, the average K for our cases of heart failure was 0.415 (0.407 for the men and 0.449 for the women). As compared with the first group, it can be seen that the Q-T interval shows greater prolongation in cases of cardiac enlargement with failure than in those without it.

After recovery from congestive heart failure, the Q-T interval, with two exceptions, exhibited a uniform shortening, relative to the heart rate. In one case there was practically no change, and in the other there was a slight prolongation. The average value for K was 0.396 with Bazett's formula and 0.379 with Ashman's formula, which was about 9 per cent less than during failure. As we pointed out above, the fact that digitalis shortens the Q-T interval has been demonstrated by several workers. Our patients had been given digitalis, and all were taking maintenance doses at the time the second electrocardiograms were taken. Stewart and Cohn[16] showed that digitalis reduces the size of the hearts of normal persons and patients with congestive heart failure. It is therefore interesting to speculate on how much the shortening of the Q-T interval after digitalis is caused by the action of the drug, per se, and how much to the reduction in the size of the heart.

SUMMARY AND CONCLUSIONS

1. In a careful study of twenty-six cases of cardiac enlargement, eleven without, and fifteen with, congestive heart failure, we have found that cardiac enlargement alone, without concomitant congestive failure, produces a significant relative prolongation of the duration of systole, as measured by the Q-T interval of the electrocardiogram, in the majority of cases, taking into due consideration the important factor of heart rate. It made no difference whether the hypertrophy affected primarily the left or the right ventricle.

2. Congestive heart failure, in addition to enlargement, produced a still greater prolongation of the Q-T interval in our cases.

3. After recovery from failure, while the patients were still under the influence of digitalis, the Q-T interval showed a relative shortening.

4. It is possible that cardiac enlargement, with longer pathways of impulse conduction and greater bulk of contracting muscle, is one of the factors responsible for the prolongation of the Q-T interval, and that digitalis may act on the duration of systole chiefly by increasing heart tone, which, in turn, brings about a decrease in the size of the heart.

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THE DEPRESSOR EFFECT OF TISSUE IMPLANTS IN HYPERTENSIVE DOGS

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IN THE course of studies involving the transplantation of kidneys to the necks of hypertensive dogs, we noted that a marked and prolonged depressor effect sometimes occurred as autolysis of the kidney began and an abscess developed at the site of the transplant. This effect could also be produced by subcutaneous implantation of 10 to 15 grams of kidney tissue.[1] To date we have implanted kidney or other tissue in a large number of experiments in dogs with nephrogenic or spontaneous hypertension and in normal dogs.

Blood pressures were recorded on these trained, unanesthetized dogs with the Hamilton manometer according to the technique previously described.[2] Normal dogs were those which, after a period of training, had a fairly constant arterial pressure of about 150/80 mm. Hg. Dogs with a persistent arterial pressure of 175/95 mm. Hg or more after a prolonged period of training were considered to have spontaneous hypertension. Nephrogenic hypertension was produced by partial constriction of the renal arteries with linen ligatures.[3] After the blood pressure of the test animals became stabilized, the various tissues were implanted subcutaneously. Daily recordings of the blood pressure were made until it returned to control levels. This was followed by triweekly recordings for a variable period.

Unless the diastolic pressure fell more than 20 mm. Hg the result was considered negative. When the diastolic pressure decreased more than 20 mm. Hg, but less than 40 mm. Hg, and the fall lasted one or two days, the result was considered slightly positive. An effect greater than this in degree and duration was considered strongly positive. In addition to the blood pressure, the heart rate, rectal temperature, and the general appearance of the animals were observed.

The tissues were implanted subcutaneously in the lumbar region, and the subcuticular fascia and skin were stitched over the implant. Asepsis was not maintained.

The following substances were used: (1) Fresh dog, rabbit, beef, and pig kidney, 10 to 30 grams;* (2) fresh dog heart, liver, or spleen, 10 to 30 grams; and (3) 10 c.c. of egg yolk or 1 to 3 grams of infusorial earth in saline suspension.

RESULTS

The effects of the various implants and injections are briefly summarized in Tables I, II, and III. Abscesses developed in nearly every instance, began to drain on the second and third day, and were usually entirely healed by the seventh day. The rectal temperature was raised

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TABLE I

EFFECT OF VARIOUS TYPES OF SUBCUTANEOUS IMPLANTATIONS ON THE ARTERIAL PRESSURE OF DOGS WITH NEPHROGENIC HYPERTENSION, AS JUDGED BY THE EXTENT AND DURATION OF THE FALL IN BLOOD PRESSURE*

TYPE OF MATERIAL IMPLANTED	BLOOD PRESSURE RESPONSE†			DEATH OF ANIMAL	TOTAL
	NONE	SLIGHT	DEFINITE		
Fresh dog kidney	21	7	14	2	44
Fresh dog kidney in small amount (1 Gm.)	4				4
Fresh rabbit kidney	4				4
Beef kidney	5	1	1		7
Pig kidney	7				7
Fresh dog heart	8	1	1	2‡	12
Fresh dog liver	7	4	1		12
Fresh dog spleen	2				2
Egg yolk	5				5
Infusorial earth	3				3

*In practically all cases fever occurred; the rectal temperature rose from about 101.5° C. to 103.5 or 105° C., usually within twenty-four hours. This was associated with cardiac acceleration. The fall in blood pressure, when it occurred, usually was not manifest until the third day, when the temperature was again approaching normal. The fever occurred not only in animals in which the blood pressure fell, but also in those in which it did not.

†Classification of response described in text.

‡In both of these dogs the blood pressure was lowered toward normal levels for some time before the animals died.

TABLE II

EFFECT OF VARIOUS TYPES OF SUBCUTANEOUS IMPLANTATIONS ON THE ARTERIAL PRESSURE OF SPONTANEOUSLY HYPERTENSIVE DOGS, AS JUDGED BY THE EXTENT AND DURATION OF THE FALL IN BLOOD PRESSURE*

TYPE OF MATERIAL IMPLANTED	BLOOD PRESSURE RESPONSE*			DEATH OF ANIMAL	TOTAL
	NONE	SLIGHT	DEFINITE		
Fresh dog kidney	2		8	1	11
Fresh dog heart muscle	2				2
Fresh dog liver		1			1
Egg yolk	1				1
Infusorial earth	4	1			5

*See footnotes of Table I

TABLE III

EFFECT OF VARIOUS TYPES OF SUBCUTANEOUS IMPLANTATION ON THE ARTERIAL PRESSURE OF NORMAL DOGS, AS JUDGED BY THE EXTENT AND DURATION OF THE FALL IN BLOOD PRESSURE*

TYPE OF MATERIAL IMPLANTED	BLOOD PRESSURE RESPONSE*			DEATH OF ANIMAL	TOTAL
	NONE	SLIGHT	DEFINITE		
Fresh dog kidney	8				8

*See footnotes of Table I

from the normal of 101.5 to 103.5 or 105° C. within twenty-four hours, and returned to normal in a day or two. The animals seldom manifested any particular depression, but frequently showed discomfort which was apparently caused by the inflamed and tender infected areas in the region of the tissue implantation. On occasion, however, the reaction was more severe, and several animals died two to six days after

implantation. There was no significant difference in these general reactions among the various groups of animals nor with the various types of implants.

In contrast to the similarity of these general effects, certain differences in the blood pressure response were apparent. In none of the eight experiments on normal dogs was any significant depressor effect noted (Table III). With dog kidney implants a definite depressor effect was obtained in fourteen of forty-four trials on dogs with nephrogenic hypertension and eight of eleven trials on spontaneously hypertensive animals. This is in sharp contrast to the results obtained with implantation of other tissues in hypertensive dogs, in which only one of fourteen trials with beef or pig kidney, one of fourteen with dog heart, and one of thirteen with dog liver gave a definite depressor effect. In none of the six trials with egg yolk and the eight trials with infusorial earth was a definite depressor response obtained in the hypertensive dogs.

DISCUSSION

Since our preliminary note on the effect of subcutaneous implantation of kidney tissue, the experiment has been repeated with modifications by other investigators. It has been reported[4] that, if special precautions are taken to avoid infection, abscess formation does not occur and the blood pressure does not fall. In rats, a reduction in blood pressure follows abscess formation, but in this animal the depressor effect appears to be nonspecific, for it occurs with implants of spleen and liver, as well as kidney.[5] Our results indicate that in the dog the reaction appears to be more specific for kidney. It would appear that, in the process of abscess formation after implantation of dog kidney, some reaction occurs which tends to reduce both nephrogenic and spontaneous hypertension. The results in spontaneous hypertension are of particular interest, for it may be more analogous to human essential hypertension than is nephrogenic hypertension.

Since the fall in blood pressure occurs on the third day, when the fever and the reaction to the abscess are on the decline, and since the depressor effect persists in some experiments for many days after the abscess has completely drained and healed, the effect probably cannot be solely the result of fever or infection. The occurrence of fever in most of the animals whose blood pressure did not fall also suggests that any fall in blood pressure is not due simply to the vasodilator effect of fever. Furthermore, we have seen a number of instances of severe infection, such as pneumonia and postoperative abscesses, in our hypertensive dog colony without changes in blood pressure.[6] Distemper, however, frequently caused the pressure to fall for some time.[2] Furthermore, a depressor effect from the injection of nonspecific materials, such as pyrogenic inulin, typhoid vaccine, etc., has been reported,[7, 8] and the blood pressure of hypertensive human subjects may fall during fevers, infections, and intoxications.[7] For example, it has been reported

that, during the induction of malaria in hypertensive patients, the blood pressure may fall and remain at a normal level for a period of days, even after the fever has subsided.[9] It was further observed that even when the pyrogenic reaction is prevented by amidopyrine, the depressor effect in hypertensive subjects is still present.[7]

A number of extracts of plants and animal tissue have been advocated for the treatment of hypertension; each has had its vogue, but none has been widely accepted.[10, 11] Kidney extracts have been employed for sundry purposes, including the treatment of hypertension, but until recently without rational or experimental basis. In some of the earlier work, in which the renal extracts were given intravenously, the effect on the blood pressure was probably a peptone reaction.

Recent developments in the study of hypertension have established a more rational basis for the use of kidney extracts in the treatment of the disease.[12, 13] Although these studies are in accord that an antipressor effect may be produced by the administration of kidney extracts, the concepts advanced as to the cause of the fall in blood pressure do not agree. Further, the methods of extraction of the kidney in the various studies are different. The extracts are still crude and require large quantities of kidney to furnish relatively small amounts of depressor material. At present there is no unanimity concerning the nature of the principle.[14] For example, one group[13] has found that it follows the protein fraction and is not an ultrafiltrate, whereas another,[12] using similar methods of preparation, reports that it is an ultrafiltrate and not a protein. The possibility that in many cases the fall in blood pressure may be spontaneous, or the result of more complete control of the patient, has not been definitely ruled out. In animals similar fluctuations in blood pressure are frequently observed, and may even occur in well-trained dogs with severe hypertension.[6] Recent studies[7, 8, 9] on the depressor reactions brought about in hypertensive subjects by nonspecific pyrogenic substances raise some doubt as to the specificity of the renal extracts previously employed.

Our own results may be ascribed to a nonspecific reaction of a similar nature. However, the absence of a depressor response in the normal dogs with kidney abscesses indicates that, in our experiments, there was no general depressor effect which might result from conditions in infection that lead to peripheral vascular collapse. We have previously noted that the factors which maintain hypertension and normal blood pressure are different, and it is well known that changes in the blood pressure, especially downward deviations, are resisted by numerous mechanisms. Normal animals appear to show a greater resistance toward depressor effects than hypertensive animals. We are, however, inclined to the view that, although this factor is of importance, it cannot be the sole cause of the difference in response between normal and hypertensive animals, for a survey of depressor actions in general shows that they operate on normal as well as hypertensive subjects. Thus, for

example, we have found that the depressor effect of late pregnancy occurs in normal as well as in hypertensive animals.[6]

It is still possible that our results can be interpreted as a nonspecific reaction operating under the peculiar conditions of the hypertensive animal. It has been shown[7] that the pyrogenic reaction, even in the absence of fever, leads to renal hyperemia. This renal hyperemia will reduce the ratio of ischemic to normal kidney tissue, and thus allow a reduction in blood pressure.[2] This would presuppose a renal mechanism in the spontaneous hypertension of the dog, and this is not yet established. If renal hyperemia is the cause of a nonspecific reduction in hypertension, our results would suggest that the liver, spleen, and heart abscesses liberate more of the effective substances than egg yolk and infusorial earth abscesses, and that kidney abscesses liberate even more. It is possible that these substances may act on other organs which participate in the hypertensive process, or may act directly on the chemical mediator of hypertension, but these possibilities will not be discussed here.

However, the alternate view has not been excluded that in abscesses produced by the implantation of fresh dog kidney a specific antihypertensive principle is elaborated or liberated. If this be so, our work indicates that 10 to 30 grams of kidney may be sufficient to produce enough material to lower the blood pressure of hypertensive dogs. To date, other workers have required large amounts of kidney for the production of their principles. In this case more potent preparations of antihypertensive principle are possible.

SUMMARY

1. The subcutaneous implantation of 10 to 30 grams of fresh dog kidney leads to abscess formation in forty-eight to seventy-two hours and frequently results in a reduction of the blood pressure of dogs with nephrogenic or spontaneous hypertension.

2. In normal dogs similar abscess formation has no appreciable effect on blood pressure.

3. Abscesses produced by implantation of fresh muscle, liver, or spleen have little or no effect on the blood pressure of hypertensive dogs.

4. The significance of these results is discussed.

We are indebted to Dr. M. Sokolow and Miss L. Friedberg for assistance in the early experiments of this study.

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Clinical Reports

A CASE OF BUERGER'S DISEASE IN AN OLD WOMAN

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THE occurrence of thromboangiitis obliterans in an old woman is sufficiently infrequent to warrant recording it.

CASE REPORT

M. C., a 68-year-old white woman, came under observation Oct. 28, 1941. Three weeks previously she had been suddenly seized with severe pain in her right leg, followed by coldness and numbness of both feet. Two weeks later intense burning pain appeared in the right second toe, and the toe turned blue. Prior to the onset of her present illness she had never had any symptoms which could have been attributed to vascular disease of the lower extremities. She had never smoked and had never suffered from any form of superficial phlebitis.

Examination.—The patient was in evident distress. No pulsation was palpable in the dorsalis pedis, posterior tibial, or popliteal artery in either leg. Excellent pulsations could be felt in both common femoral arteries. Oscillometric readings were zero up to the level of the knees. At a room temperature of 24.0° C., the surface temperature of the great toes was 25.0° C. After the administration of 50 mg. of procaine intrathecally, anesthesia of both feet occurred, but the surface temperatures rose only 1.3 degrees. There was extreme pallor of both feet on elevation, and the right foot was edematous. There was ulceration of the right second and left fourth toes. The ulcerated right second toe was exceedingly sensitive to the slightest manipulation, and was in a state of impending gangrene. There were no areas of acute or healed superficial phlebitis. She presented clinical evidence of generalized arteriosclerosis. Her blood pressure was 238/134.

The blood Wassermann reaction was negative. The erythrocyte count was 3,800,000, and the hemoglobin was 67 per cent. The albumin/globulin ratio was 4.1/4.3. The sugar and nonprotein nitrogen levels in the blood were 129 and 28 mg. per cent, respectively. The spinal fluid was normal.

A diagnosis of bilateral, acute thrombosis of an arteriosclerotic popliteal artery was made.

Within twenty-four hours of her admission to the hospital the right second toe had become frankly gangrenous. In an attempt to alleviate the now intractable pain, an adventitial stripping of the superficial femoral artery and ligation of the accompanying vein were performed. At the time of operation I was impressed by the absence of significant atheromatous involvement of the wall of the occluded femoral artery. The next morning there was a distinct diminution in pain and sensitivity to manipulation in the gangrenous toe. However, the gangrene continued to spread. By the tenth hospital day the entire foot had become gangrenous, pain had recurred, and a thigh amputation was performed as a life-saving measure. However, that evening the left foot became suddenly gangrenous, and three days later the patient died.

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The following is a detailed report of the microscopic examination of sections taken from the arteries of the amputated leg. The description is by Dr. F. Preuss, of the Laboratory of Pathology at Mt. Sinai Hospital.

Popliteal Artery and Vein.—The lumen of the artery is occluded by fairly dense connective tissue containing a large number of fibroblasts and mononuclear cells. A few small vascular spaces lined with epithelium and filled with erythrocytes are seen. These apparently represent areas of recanalization. The media shows a diffuse infiltration with lymphocytes and mononuclear cells. The intima and internal elastic lamella are indistinct. The adventitia is composed of very dense connective tissue which is infiltrated with lymphocytes and mononuclear cells; it contains numerous vasa vasorum which exhibit similar chronic inflammatory changes. The popliteal vein shows similar inflammatory changes. The intima is thickened by granulation tissue. The media is interrupted by connective tissue showing numerous fibroblasts and round cell infiltration. The adventitia presents a picture similar to that of the adventitia of the artery. The artery and vein are adherent to each other by dense inflammatory connective tissue.

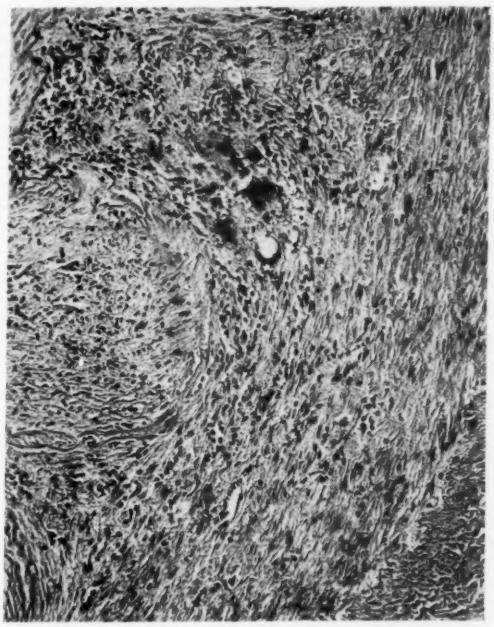

Fig. 1.—Posterior tibial artery. (Dr. F. Preuss)

The lumen of the artery is occluded by cellular granulation tissue containing only a few small capillary vascular spaces. The internal elastic lamella is indistinct and fragmented. The media is markedly infiltrated with lymphocytes and monocytes. Several giant cells are present, indicating a chronic and subacute inflammatory process. There is also increased vascularity of the media.

Posterior Tibial Artery.—See Fig. 1.

Posterior Tibial Vein.—See Fig. 2.

Anterior Tibial Artery and Vein.—See Fig. 3.

Final Diagnosis: Thromboangiitis obliterans (Buerger's disease).

In addition to the fact that the patient was a woman, the interesting point is that she reached the age of 68 years before the peripheral vascular disturbance became manifest clinically. This attests that a

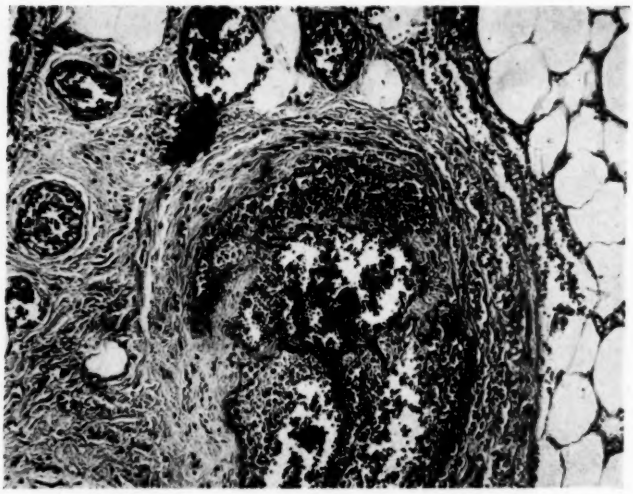

Fig. 2.—Posterior tibial vein. (Dr. F. Preuss)

The lumen is occluded by an apparently recent, red thrombus, consisting mainly of erythrocytes and a few threads of fibrin. The endothelial lining of the intima is stripped off in places. The media shows diffuse infiltration by polymorphonuclear leucocytes. There are also a marked periphlebitis and an increase of vasa vasorum in the adventitia.

Fig. 3.—Anterior tibial artery and vein. (Dr. F. Preuss)

The lumen of the artery is reduced to a slit-like space by fibrous tissue which in one sector, shows a marked cellular reaction. The internal elastic lamella is recognizable only in the upper sector. There is moderate cellular infiltration of the media. In the upper right-hand corner the small residual lumen of the vein is seen. Artery and vein are matted together tightly by old granulation tissue. The line of cleavage cannot be made out.

remarkably effective collateral circulation may develop in cases of thromboangiitis obliterans without the benefit of therapeutic assistance. In line with this observation is the case of a 65-year-old man with Buerger's disease whom I saw recently. In this instance the first clinical evidence of the vascular disability was also the sudden appearance of pain in the leg and foot, followed by gangrenous ulceration. Microscopic examination of the arteries in the amputated leg revealed lesions characteristic of long-standing thromboangiitis obliterans, with recent, major thrombosis involving the popliteal and lower femoral artery.

The author acknowledges his indebtedness to Dr. S. S. Sidenberg, the attending physician in this case.

DISSECTING ANEURYSM OF THE ABDOMINAL AORTA

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IN A RECENT paper on dissecting aneurysm, Rogers[1] remarks that, until 1933, only six cases of this condition had been discovered ante mortem. Since then, thirty-four additional cases have been reported. In view of the many outstanding manifestations of this disease, it is remarkable that more cases have not been reported. The following case is presented to emphasize the important signs and symptoms of this disease, and because it is the second case in which a dissecting aneurysm beginning in the abdominal aorta has been diagnosed before death. It is interesting that the diagnosis in this case was made by an intern, and overlooked by men of far greater experience. This is not a criticism of these men, but rather an indication of the lack of awareness of the average practitioner to the clinical features of dissecting aneurysm.

CASE REPORT

The patient was a white man, 64 years of age, who was admitted to the hospital because of severe, recurring radiating pain of over three years' duration. For more than thirty years the patient had suffered from vague abdominal distress, but in the preceding three years a new symptom became prominent. The symptom was pain, described as agonizing and viselike, which always began in the epigastric or lower substernal region, radiated upward to involve the entire chest and back, and then spread down the arms as far as the finger tips and upward to the neck and head as far as the vertex. This radiation was fairly constant, and the distribution was symmetrical. At first the patient suffered at irregular intervals, especially, but not always, after strenuous exertion. At the beginning of the illness the pain lasted only a few minutes, but later it occurred with increasing frequency and severity, and lasted as long as thirty minutes. There were intervals of days or even weeks when this agonizing pain did not occur. The patient knew of nothing that would relieve the pain, but he remarked that he tried to calm the "torture" by compressing and rubbing his abdomen and chest; however, this produced no relief. For eighteen months a mass in his abdomen had been evident, and was increasing in size.

The past history revealed that the patient had had left-sided, spontaneous hydropneumothorax from a "ruptured emphysematous bleb" which disappeared without complications. There was also a history of chronic atrophic gastritis, with achylia gastrica, bilateral direct inguinal hernia (not operated on), and some "duodenal disturbance" of unknown origin. Three years earlier he had been examined at the Mount Sinai Hospital of New York City. The roentgenologic reports from that institution revealed that he had a large tortuous aorta, but no diagnosis of aneurysm was made. Hypertension and severe arteriosclerosis were also diagnosed at that time.

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Physical examination revealed a tall, thin, elderly, and chronically ill white man. The head was essentially negative, as were the eyes, ears, and nose. He had pyorrhea alveolaris and many carious teeth. The chest was asthenic and the ribs were very prominent. A marked depression at the lower portion of the sternum, probably occupational in origin, was noted. The patient was an architect, and had worked over a draftsman's board for years. The lungs were normal. The heart was enlarged to the left (approximately 2 cm. beyond the left midclavicular line, fifth intercostal space); the rhythm was normal, and auscultation revealed a systolic and a diastolic murmur in the aortic region which were transmitted upward and downward along the right sternal margin. The pulse rate was 76, and the pulse was full and strong. His blood pressure was 250/170 in the left arm and 256/174 in the left leg. Within the abdomen, just below the epigastric region, there was a very interesting tumor about the size of a grapefruit. The tense mass, a practically immovable tumor and with no expansile pulsation, extended below and to the left, and above and to the right of the umbilicus. No thrill was palpable, but there seemed to be a slight, inconstant systolic murmur. The abdominal wall was very thin, and there was a direct inguinal hernia on each side. The arteries were very hard and tortuous, particularly the femorals, which were pipelike and at least 2 cm. in diameter, and could be easily palpated as they coursed over the pubic rami. The other systems were essentially negative.

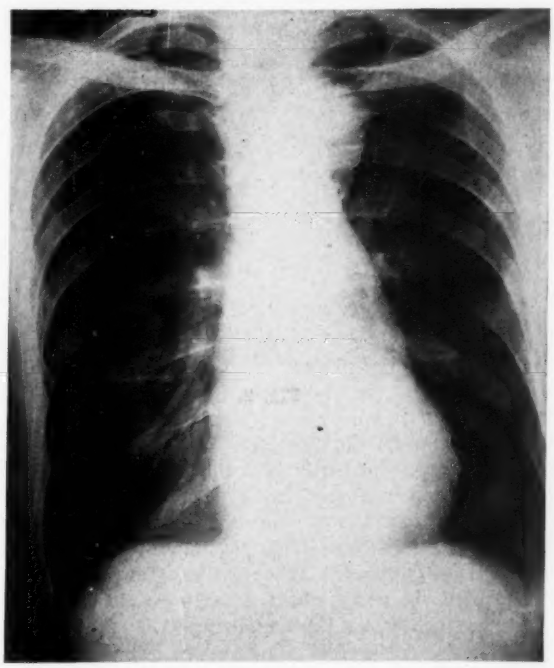

Fig. 1.

At the time, the provisional diagnosis was "Aneurysm of the abdominal aorta, arteriosclerotic in origin and dissecting and saccular in type."

Laboratory Examination.—The leucocyte count was 7,300, with a normal differential count. The erythrocyte count was 4,320,000, with 86 per cent hemoglobin (12.6 Gm., Sahli). The Kolmer-Wassermann reaction was negative. The urine showed an occasional hyaline cast. Electrocardiographic studies, unfortunately, were not made. Roentgenologic examination included stereoscopic and oblique

chest films and gastrointestinal study. The latter showed external pressure on the lesser curvature of the stomach. The chest roentgenograms showed (Figs. 1 and 2) enlargement of the cardiac shadow, especially of the left ventricular portion, and a greatly dilated and tortuous aorta which took the shape of the letter S; the arch was represented by the upper half of the letter, and the thoracic portion by the lower half. The lateral deviation from the midvertebral line to the left lateral border was 9 cm. at the level of the ninth dorsal vertebra. In this region the aorta showed its greatest transverse diameter (4 to 5 cm.). These observations were essentially the same as those made at Mount Sinai Hospital.

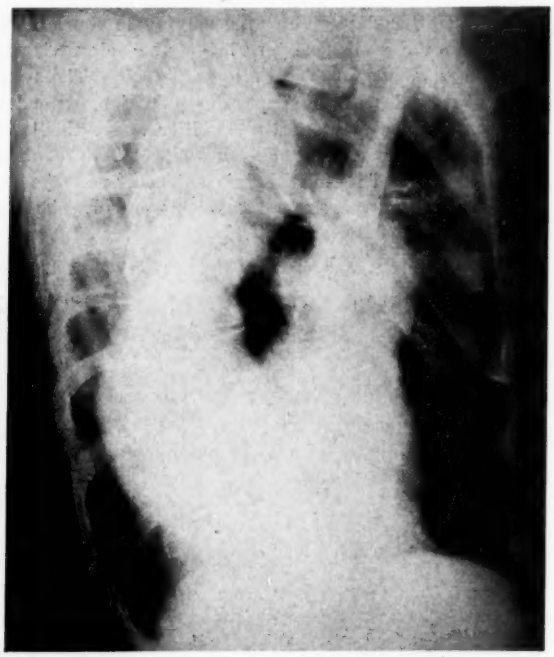

Fig. 2.

Subsequent Course.—During the first five days of hospitalization the patient was up and about. He complained only of a constant, dull, abdominal pain. Never did he have the severe pain mentioned in the "present illness." The preoperative diagnosis of the surgeon was "pancreatic or peritoneal cyst or possible aneurysm of the abdominal aorta." The last diagnosis, in view of the operation performed later, apparently held little favor. At operation, "an aneurysm was found just above the bifurcation of the aorta, about 8 to 10 cm. in diameter, with one small sacculation at its right border, on the lateral aspect." No surgical procedure was attempted on this lesion. On the day after the operation the patient complained of pain in the abdominal wound. His second day was uneventful, but, on the night of the third postoperative day, at 11 o'clock, he complained of a sudden, severe pain in the abdomen, and died before the intern arrived.

Post-Mortem Examination (performed by Dr. W. Cook).—Only the main gross autopsy observations in regard to the aneurysm and arterial system are discussed. When the abdominal cavity was opened it was found to contain a great deal of coagulated blood. The abdominal aorta presented a large rent at its beginning; this extended downward several centimeters, beyond the level of the renal vessels. The entire vessel, though collapsed post mortem, had been diffusely enlarged, and

anterolaterally the wall showed sheath dissection from the region above the renal vessels to just above the bifurcation. The adventitial portion of the aneurysm was over 10 cm. in diameter, and contained a large laminated thrombus; its proximal level communicated with the lumen of the aorta through a large opening. The internal surface of the aorta showed marked atheromatous degeneration and ulceration throughout, especially in the abdominal portion, and also some ulcers 2 to 3 cm. in diameter, with deep overhanging walls filled with thrombi and lipoid material. The thoracic aorta was markedly dilated and tortuous, and the lower half extended far into the left thoracic cage. There was also marked arteriosclerosis involving the muscular arteries. Other important associated abnormalities were left ventricular hypertrophy and nephrosclerosis.

COMMENT

Excellent discussions of the etiology and pathology of this condition have been presented in other papers. In this case, the outstanding etiologic factors were arteriosclerosis, hypertension, and probably occupational trauma. Repeated pressure of the draftsman's board over a period of many years directly against the abdomen and sternum and indirectly on the atheromatous aorta might have been an important factor in the development of the aneurysm; however, one must admit that it might have been coincidental. This case again emphasizes the importance of severe oppressive pain with radiation. It is difficult to explain the wide distribution of the pain in this case (probably a great deal of it arose from the arch and thoracic aorta), but radiation of pain is one of the most common symptoms, and occurs in practically every case, with the exception perhaps of some of the more fulminating lesions.

Dissecting aneurysms rarely reach the dimensions of the one described, but in this regard there was a similarity to Bahrdt's[2] case, in which there was a pulsating tumor, the size of a hen's egg, above the umbilicus.

This case also shows that dissecting aneurysm is not necessarily an "acute castastrope," as many are inclined to believe. The case of Rogers[1] and several others support this fact, and the pathologic reports are confirmatory. From the history, one might say that the dissection probably began at least three years prior to the patient's death.

SUMMARY

A case of aneurysm of the abdominal aorta, diagnosed ante mortem, is reported; this is the thirty-fifth dissecting aneurysm, and the second beginning in the abdominal aorta, on record.

The author wishes to thank Dr. Roberto for the roentgenograms, and Dr. Buel Latcher. The patient was originally under the care of Dr. Latcher, who, from the beginning, agreed with the author's diagnosis.

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INTRAUTERINE TRAUMATIC LESIONS OF THE HEART

Report of a Case, With Autopsy

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NONPENETRATING injuries of the chest wall which produced cardiac lesions in adults have been reported by Kahn and Kahn,[1] Kissane, Fidler, and Koons,[2, 3, 4] Bright and Beck,[5] Beck,[6] and Moritz and Atkins.[7] These reports establish trauma to the heart as a cause of death in nonpenetrating injuries of the chest wall, and are supported by anatomic and experimental evidence. Intrauterine lesions of the heart produced by trauma to the maternal abdomen have not been reported. The following case is presented to illustrate this condition.

CASE REPORT

The patient, a 17-year-old primigravida, was under obstetrical care during her entire prenatal period, during which time her weight gain had been 18 pounds. Three days before her estimated date of confinement she had her last prenatal examination, at which time the baby was alive, as evidenced by fetal motion and fetal heart tones in the left lower quadrant at the rate of 136 per minute. Her entire prenatal course had been uneventful; the blood pressure was within normal limits, the urine on all examinations was negative for albumin and sugar, and the blood serologic reactions were negative.

Six hours after her last prenatal examination she was in a severe automobile accident. The car in which she was riding as a passenger was struck from the left side by another car. She was thrown a distance of about ten feet from the car through the right car window, and struck her abdomen on the curb. She was taken to a hospital for treatment of lacerations of the forehead and right hand and severe contusions of the abdominal wall. In the accident room of this hospital it was noticed that the fetal motion and heart tones were absent. She was kept under observation at this hospital for two days, and, on the third day, which was her estimated date of confinement, she was brought to White Cross Hospital.

Upon admission, the uterus was enlarged to the size of a full-term pregnancy, but death of the fetus was evidenced by the absence of fetal motions and heart tones. The uterine contractions were strong and regular, and occurred at three-minute intervals. Rectal examination showed that the cervix was effaced, was dilated 2 cm., and that the head was at the level of the ischial spines. The labor was conducted under sodium amytal and scopolamine analgesia. Delivery was accomplished by prophylactic forceps extractions, preceded by a right mediolateral episiotomy under nitrous oxide-ether anesthesia. The baby was a full-term still-born female, and weighed 7 pounds. The duration of labor was eleven hours and thirty minutes; the first stage lasted ten hours and forty-five minutes, the second stage, thirty-five minutes, and the third stage, ten minutes.

Autopsy.—Autopsy was performed on the stillborn child two hours after birth. The body was that of a well-developed and well-formed female; it measured 48 cm.

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in length and weighed 7 pounds. There were no malformations or deformities, the skin was intact and of normal color, and the usual short portion of umbilical cord was attached and slightly dried.

Upon opening the abdomen the peritoneum was found to be smooth and glistening and free from petechiae or ecchymoses; there were approximately 5 c.c. of a clear amber fluid free in the peritoneal cavity. The various viscera were in their normal positions, and the liver extended the usual distance below the right costal margin. There was no evidence of rupture of the liver; no subcapsular hematomas were found, and the cut surface of the liver was normal. The gall bladder, pancreas, and spleen were normal. The kidneys, ureters, and urinary bladder were entirely normal. Both adrenal glands were normal for a newborn. The pelvic viscera were normal. The lymph nodes of the mesenteric and retroperitoneal groups were not enlarged. There was no retroperitoneal hemorrhage, and the lumbar spine and bony pelvis were normal.

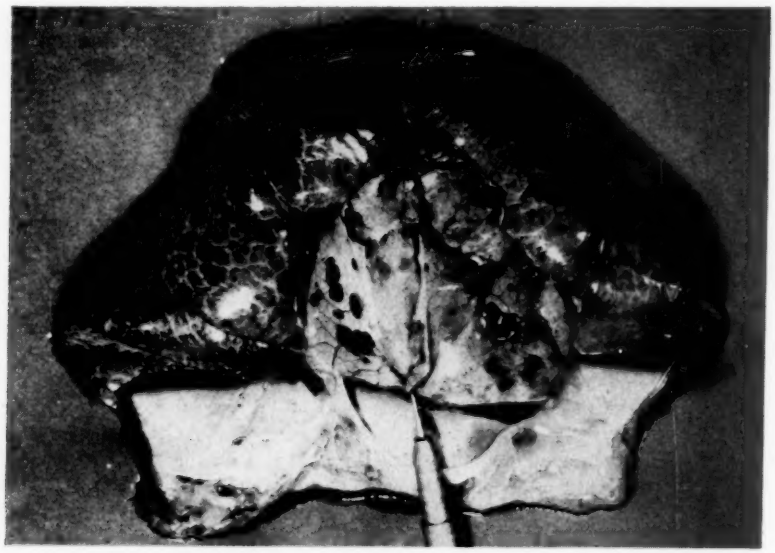

Fig. 1.—Lungs, pericardium, and diaphragm, showing hemorrhages over the external pericardial surface and mesial portions of the adjacent lungs.

Upon opening the thoracic cavity by elevation of the sternum, both pleural cavities were found to contain approximately 10 c.c. of bloodtinged fluid. The pericardial sac was rounded and widened to a transverse diameter of 3½ cm. The thymus was of the usual size and shape, with the right lobe extending downward as a thin prolongation just over the upper portion of the pericardial sac. There was no evidence of hemorrhage into the thymus or mediastinum. There was no fracture or dislocation of the ribs, sternum, or dorsal spine, but on the lateral surface of the right parietal pleura there were several small petechial areas.

The lungs were unexpanded, and, over the pleural surfaces of the middle and upper lobe of the right lung, especially over its mesial surface, there were scattered areas of petechiae. There were similar areas in similar positions over the mesial surface of the left lung. Cut sections of the lungs showed no evidence of expansion and no interstitial hemorrhage, and the trachea and bronchial tree were free and patent.

The external surface of the pericardial sac presented multiple areas of fresh hemorrhage, extending on the right side down to the level of the diaphragm (Fig. 1). The pericardial sac was found to contain a markedly increased amount of hemorrhagic fluid. On the inner surface of the pericardial sac there were multiple areas of hemorrhage similar to those on its external surface. No gross tears of the pericardium were found. The heart presented multiple areas of hemorrhage over its anterior surface, and, involving the descending branch of the left coronary artery and vein for a distance of 2 cm., there was an area of hemorrhagic extravasation measuring 5 mm. in diameter (Fig. 2). Over the posterior surface of the heart, extending downward along the distribution of the descending rami of the circumflex artery, there were similar areas of hemorrhagic extravasation. Similar hemorrhagic material was found along the course of the right coronary artery. No contusion of the myocardium was apparent from the epicardial surface. Dissection of the coronary arteries failed to demonstrate a point of actual vessel rupture; the hemorrhage described above appeared as a dense extravasation into the epicardium. The coronary arteries showed no evidence of congenital sclerosis. Upon opening the heart, the various valves and chambers were found to be normal, and there was no evidence of endocardial hemorrhage or myocardial contusion.

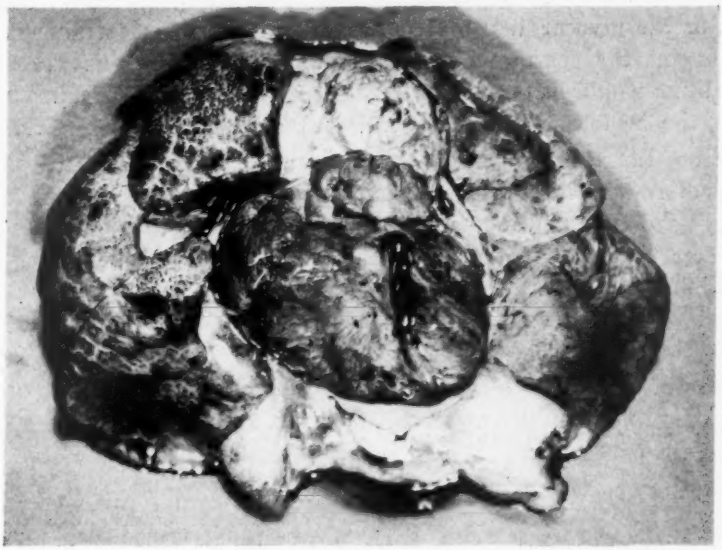

Fig. 2.—Lungs and heart after opening the pericardial sac, showing hemorrhage over the epicardial surface and along the left coronary vessels.

Examination of the head showed no lesions of the scalp or calvarium, the dura and arachnoid were normal and free from hemorrhage and tears, and the brain was grossly normal.

The anatomic diagnosis was traumatic heart disease, characterized by pleural, pericardial, and epicardial hemorrhage, with hemopericardium, hemothorax, and unexpanded lungs.

Microscopic sections of the lungs showed no expansion, no interstitial hemorrhage, and occasional alveoli filled with coagulated fluid; the hemorrhage on the pleura appeared as infiltrating hemorrhagic extravasations elevating and sometimes penetrating the pleura.

Microscopic sections of the pericardial sac showed hemorrhagic infiltration of the fibrous external tissue, without tears; on the inner surface, this hemorrhage elevated and penetrated the endocardial lining. Sections of the heart itself showed extensive extravasation of fresh blood cells throughout the epicardial tissue about the coronary arteries, with hemorrhagic invasion of the adventitial, and, in some cases, of the external medial, portions of these arteries and veins. The inner medial layers and intima of these vessels appeared normal in the various sections. There was only slight invasion of the adjacent myocardium by this recent hemorrhage. There was no evidence of organization in any of the hemorrhagic areas. Sections of various other organs and tissues showed no pathologic changes.

The final diagnosis was traumatic heart disease characterized by acute hemorrhagic extravasation into the epicardium along the course of the coronary vessels, additional traumatic hemorrhages into the pericardium and pleura, hemopericardium, hemothorax, and death in utero with unexpanded lungs.

DISCUSSION

The cardiac, pericardial, and pleural lesions in this case were entirely comparable, and were similar to those in previously published cases of traumatic heart disease. Epicardial lesions are more common than lesions of the myocardium and pericardium. Hemopericardium is also frequent in this condition. The trauma manifest in this heart and pericardium would be considered quite extensive even in the adult heart, so that the hemorrhage could be properly designated as massive.

The fact that there was an apparently normal heart and baby a few hours before the injury, the history of a severe, direct blow to the maternal abdomen and uterus, and the discovery that the baby was dead soon after the injury establish a sequence of events which is entirely compatible with the autopsy observations.

SUMMARY

A case of intrauterine cardiac injury which was produced by a nonpenetrating blow to the maternal abdomen and resulted in the death of the fetus is reported.

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Abstracts and Reviews

Selected Abstracts

Friedman, M., and Kaplan, A.: Studies Concerning the Site of Renin Formation in the Kidney. IV. The Renin Content of the Mammalian Kidney Following Specific Necrosis of Proximal Convoluted Tubular Epithelium. J. Exper. Med. 77: 65, 1943.

The admission of tartrate to adult rabbits was found to produce in some of them, a profound and widespread necrosis of the proximal convoluted tubular epithelium without affecting the other portions of the nephrons.

The markedly damaged kidneys were found to be almost completely devoid of pressor substance (renin), indicating that in the mammalian kidney, the epithelium of the proximal convoluted tubules is concerned in the formation or storage of renin.

AUTHORS.

Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Altheromatosis in an Omnivorous Animal, the Chick. Arch. Path. 34: 937, 1942.

Twenty-four 10-day-old cockerels were divided into two equal groups. One group was fed an adequate diet for fifteen weeks. The second group was placed on the same diet plus 2.5 to 5 per cent cholesterol in cottonseed oil. In none of the control cockerels did vascular lesions develop. In seven of the twelve cholesterol-fed birds (the remaining five dying within eight weeks) atheromatous deposits developed in the aorta. Of these seven chicks, three had intimal atheromatous lesions in the coronary arteries with resultant narrowing of the vessel lumens; two of the seven showed similar changes in the splenic arteries. The hearts of the cholesterol-fed birds weighed slightly more in proportion to the body weights than did those of the control series.

The chick is an omnivorous animal in which experimental atheromatosis can be readily produced by feeding a high cholesterol diet. The induced arterial lesions resemble the earliest spontaneous atheromatosis which develops with advanced age in chickens.

AUTHORS.

Krafka, J., Jr.: A Heretofore Unrecognized Mechanical Principle Effective in Aortic Sclerosis. Arch. Path. 34: 965, 1942.

By using the formulas of mechanical engineering for stress in the walls of thin-walled cylinders, it is possible to relate stress in the aortic wall to blood pressure values.

Calculated values for systolic and diastolic pressures fall well within the hollow portion of the exponential curve obtained by stretching strips of aortas on the serigraph.

Percentage extensibility of the strips of aortas within the stress equivalents for systolic and diastolic pressures is consistent with the normal stroke volume considerations.

With aging, fibrosis, and sclerosis, there is a tendency to convert the plastic cylinder into a rigid one. A redistribution of force vectors accordingly follows the rivet rule, and hence a normal blood pressure may become an effective agent of rupture.

AUTHOR.

Swingle, W. W., Remington, J. W., Kleinberg, W., Drill, V. A., and Eversole, W. J.: An Experimental Study of the Tourniquet as a Method for Inducing Circulatory Failure in the Dog. Am. J. Physiol. **138:** 156, 1942.

The tourniquet method for producing shock, in which both hind legs were constricted by heavy-walled rubber tubing tightly tied around the hips for a period of five hours, has been studied in a large series of dogs.

Of twenty-five untreated control animals, all but one died in shock following the release of the constrictions. The survival periods ranged from three to twenty-seven hours. Associated with the shock condition was a marked swelling of the injured legs, an intense hemoconcentration, and a plasma volume reduction of 49 per cent.

In all animals in which leg infections were prevented by proper antiseptic treatment, the snug bandaging of both legs prior to, or immediately after removal of the constrictions, successfully prevented shock. While shock was prevented by the bandaging, the legs were paralyzed and recovered but slowly.

A plasma transfusion of 25 c.c. per kg. body weight, given immediately after release of the constrictions or later, failed to prevent hemoconcentration, and did not prevent death in nine of twelve dogs.

The same amount of plasma, divided into five doses of 5 c.c. per kg. body weight each, and transfused intermittently over a seven-hour period, prevented shock in all of seven dogs. This positive effect could not be correlated with hemodilution changes.

AUTHORS.

Eyster, J. A. E., and Meek, W. J.: Cardiac Injury Potentials. Am. J. Physiol. **138:** 166, 1942.

The potential time curve, derived from an injured region of heart muscle by the use of the suction electrode, is remarkably similar in contour and magnitude when recorded from different regions of the same heart, from different animals of the same species, and even from animals widely separated in the animal scale. It represents a local potential change which does not involve the normal muscle contiguous to the injury, although a potential field develops in a conducting field which surrounds it on all sides. The contour and magnitude of the curves differ little in extrasystoles as compared with normal beats, in contrast to the marked differences in unipolar and differential potential time curves in these two circumstances.

The change in an injured region from a negative potential to a positive potential, which occurs when the muscle contiguous to the injury enters into activity, is due to some process in the contiguous uninjured muscle or at the boundary between the injured and uninjured muscle. The start of this potential change at all surface regions of the ventricle precedes the rise of intraventricular pressure by an interval which varies with the location of the injury. At each local region, its onset precedes the onset of local or fractional contraction of the region by an approximately constant interval.

The possible relation of the start of the injury activity potential to he ''excitation process'' or ''impulse'' in the contiguous active muscle is discussed.

AUTHOR.

Rosen, S. R., and Smith, K. L.: The Role of Heart Disease in the Psychoses of the Senium. Am. J. M. Sc. 205: 48, 1943.

The cardiovascular status of forty-three cases of psychoses in the senium was carefully evaluated.

Venous pressure and arm-to-carotid circulation times were determined.

Twelve cases had advanced cardiac disease and showed markedly abnormal values, fifteen cases had minimal organic heart disease without symptomatology; and sixteen had no demonstrable organic heart disease. These last two groups had normal venous pressures and very moderately elevated arm-to-carotid circulation times.

The significance of the above findings is considered, and the role of arteriosclerosis discussed as a possible cause for the moderately elevated circulation time.

It is concluded that cardiac disease plays a minor role, if any, in the psychoses of the senium in which obvious advanced heart disease is not present.

AUTHORS.

Tuttle, W. W., and Templin, J. L.: A Study of Normal Cardiac Response to Water Below Body Temperature With Special Reference to a Submersion Syndrome. J. Lab. & Clin. Med. 28: 271, 1942.

On the basis of data collected from sixty-eight college women, the following conclusions are drawn concerning the effects of submersion in water:

Submersion in water of swimming pool temperature causes a drop in the heart rate of normally adjusted persons.

The amount of decrease in heart rate due to submersion varies directly with the resting rate.

Failure to experience a decrease in heart rate when submerged in water below body temperature is due to a lack of emotional adjustment (fear) or to a failure to compensate physiologically.

Where emotional factors are controlled, failure to experience a significant drop in pulse rate during submersion in water below body temperature indicates sensitivity to the water.

It is suggested that the conditions causing a failure to make normal adjustments to submersion in water be called the "submersion syndrome."

AUTHORS.

Reingold, I. M., Neuwelt, F., and Necheles, H.: Circulating Time in the Human Being and in the Dog as Affected by Fasting and by Meals. J. Lab. & Clin. Med. 28: 289, 1942.

The circulating time was determined in a group of human subjects and in dogs. The sodium cyanide method of Loevenhart and associates was employed. During the fasting condition considerable variations of circulating time were found in the human being and in the dog, and following meals the same or somewhat greater variations in circulating time were obtained. The authors' results indicate no significant or uniform changes in circulating time in any one direction in either the fasting or the postprandial state. The nature of the meal did not seem to determine changes in circulating time. The significance of the findings and the discrepancy of the results from those of other workers are discussed.

AUTHORS.

Simonson, E., and Enzer, N.: Physiology of Muscular Exercise and Fatigue in Disease. Medicine 21: 345, 1942.

The material reviewed shows that there is a quantitative rather than a qualitative difference of physiologic processes in exercise in disease. The limit to which they

can be increased is depressed, and this limit is reached more rapidly in disease. This is due to the fact that many mechanisms involved in muscular exercise become compensatory during rest in pathologic conditions. Therefore, these mechanisms are no longer available to their full extent to meet the demands of exercise; consequently working capacity is reduced or, what is the same by definition, fatigability is increased. Naturally, the impairment of various functions as well as the involvement of compensatory mechanisms vary in different diseases. The patient, naturally, realizes his diminished working capacity as subjective fatigue. This review attempts to show that fatigue and disease are intimately related. This relationship explains why fatigue is the most common complaint of disease.

AUTHORS.

Scherf, D., and Terranova, R.: Electrocardiographic Studies of the Displacement of S-T Segment in Experimental Thoracic Contusion. Rev. argent. de cardiol. 9: 157, 1942.

The appearance of a displacement of the S-T segment (high or low take-off) in the electrocardiogram, following blunt trauma to the precordium was studied in twenty-five cats. The displacement was obtained in fifteen animals. It disappeared within ten minutes. It is suggested that it is caused by a direct injury to the superficial layers of the myocardium. A high or low take-off of the S-T segment, appearing later, or persisting longer after the trauma, is probably due to a complication, like a pericarditis.

AUTHORS.

Luisada, A.: On the Value of Mechanical and Acoustic Registration in the Diagnosis of Bundle Branch Block. Rev. argent. de cardiol. 9: 169, 1942.

A clinical case is described in which mitral insufficiency due to rheumatic endocarditis and fibrosis of the myocardium are present.

The electrocardiogram of the patient indicated a right bundle branch block. On the contrary, the acoustic and mechanical records, as well as the fluoroscopy, gave evidence of the delayed contraction of the left ventricle.

A third heart sound was present during the descending branch of the V wave of the venous tracing. A discussion on the possibilities of extra sounds occurring in patients with bundle branch block led to the conclusion that it was impossible to ascertain whether or not it was an opening snap of the mitral valve. The diagnosis of mitral stenosis was, therefore, not supported by the records.

A wide bilateral lesion of the bundle branches should be admitted. In spite of the predominance of the lesion on the left side, the hypertrophy of the right ventricle due to the mitral defect gives to the electrocardiogram the "right-side" type.

The author wishes to call special attention to the importance of the mechanical and acoustic records in order to determine the particular side of a bundle branch block. The electrocardiogram should only point out the existence of widespread lesions below the His bundle.

A dissociation in the C wave of the venous tracing illustrates the existence of two components of it, each related to the activity of one ventricle.

AUTHOR.

Wilburne, M., and Langendorf, R.: The Significance of the Electrocardiogram With Prominent S Waves in Leads I, II, and III. J. Lab. & Clin. Med. 28: 303, 1943.

Electrocardiograms exhibiting prominent S waves (final inverted phase of the QRS complex measuring 25 per cent or more of the upright phase) in Leads I, II, and III were present in 84 cases of 1,850 consecutive electrocardiograms reviewed.

In 41 of these cases definite electrocardiographic abnormalities, such as left ventricular preponderance, right ventricular preponderance, combined right and left ventricular strain, myocardial infarction, and nonspecific abnormal patterns were found. In 8 others, questionable abnormalities were present.

In 35 cases no other deviations from the normal pattern were observed and these were regarded as the otherwise normal S type of electrocardiogram. The criteria employed in this deduction are described. In 19 of these cases no demonstrable heart disease was present; in 3 the clinical findings were inconclusive; and in 13 there was clinical evidence of heart disease.

It is concluded that electrocardiograms exhibiting prominent S waves in Leads I, II, and III are more common in patients with evidence of heart disease than in normal persons in the population of an electrocardiographic laboratory. However, in an otherwise normal electrocardiogram the S type may be a normal variant, but before this decision is made the case should be thoroughly investigated.

AUTHORS.

Currie, G. M.: Transient Inverted T Waves After Paroxysmal Tachycardia. Brit. Heart J. 4: 149, 1942.

A case of recurrent paroxysmal tachycardia in a girl with neurocirculatory asthenia is described; at the time of first observation she was 13 years of age and is now 16; serial cardiograms during and after each attack showed transient inversion of the T waves and a lowering of the S-T interval in one series; there was a return to normal in each case in a month; the degree of the inversion is probably affected by the duration of the attack. The relative importance of the clinical over the cardiographic findings in giving a prognosis in such cases is stressed, and a possible cause of the inversion is put forward.

AUTHOR.

Cooke, W. T., and White, P. D.: Prognosis in Paroxysmal Tachycardia and Paroxysmal Auricular Fibrillation. Brit. Heart J. 4: 153, 1942.

When the cardiovascular system is normal, attacks of paroxysmal tachycardia are uncomfortable, but relatively unimportant incidents.

The probability of any attack ceasing is extremely good, but the occurrence of an attack in a patient seriously ill must be regarded with some apprehension, and the occurrence of heart failure as a result of the attack may lead to the formation of intracardiac thrombi and subsequent emboli.

The occurrence of paroxysmal auricular tachycardia in apparently healthy persons seems to have no effect upon the prospect of their longevity. When occurring late in life, the prognosis, in general, is that of the underlying heart disease, if present.

Paroxysmal auricular fibrillation is probably common. When occurring in patients below the age of 40 years, it may be considered as having no prognostic significance, while in later life the occurrence of fibrillation may, in some cases, be the first sign of serious heart disease.

It is impossible to forecast with any certainty either the frequency or the duration of the attacks of paroxysmal auricular tachycardia and fibrillation.

AUTHORS.

Gilson, A. S., Jr.: The Locus and the Nature of the A-V Pause in the Spread of Cardiac Activation. Am. J. Physiol. **138:** 113, 1942.

It is concluded that an "excitation time" theory may be used to explain the delay normally occurring in the transmission of the cardiac impulse across the atrioventricular junction in the turtle heart. Ventricular excitation normally does not

occur during or because of the arrival and rise of the atrial action potential, but during the period of electrical recovery of the atrium. Long atrioventricular delays may involve serial activation of several elements thus multiplying the single junctional pause found in the normal heart.

AUTHOR.

Hunter, A., and Lipscomb, J. M.: Congenital Pulmonary Atresia With Cerebral Thrombosis and Hemiplegia. Brit. Heart J. 4: 124, 1942.

Cerebral manifestations in pulmonary atresia and stenosis are well recognized. They have been attributed either to paradoxical embolism, or to cerebral thrombosis associated with the polycythemia. Hemiplegia and epileptiform attacks are recorded by the authors, which were shown at necropsy to be due to cerebral thrombosis. Their transient nature may be explained by the absence of softening of the brain although there was such extreme distension and thrombosis of the cerebral veins.

AUTHORS.

Bremer, J. L.: Transposition of the Aorta and the Pulmonary Artery: An Embryologic Study of Its Cause. Arch. Path. 34: 1016, 1942.

Transposition of the aorta and the pulmonary artery is the common factor in many anomalies of the heart, and as such should be the result of some slight and easily produced variation from the normal course of development. Models and drawings of human hearts of 5 mm. and less show great differences in shape, especially of the bulbar region. The lower part of the bulb is transformed into the right ventricle by the outgrowth of sinusoids, sprouting earliest and most profusely from the convex surface of some acute curve. The sharpest curve in the normal bulb points downward and forward, and the spongy substance of the right ventricle, therefore, is chiefly on the ventral and apical walls. In a few of the younger hearts shown, the sharpest curve points downward and backward or dorsally, and in one human embryo studied, the sinusoids, which are just developing, are found on the apical and dorsal walls of the ventricle. Continued growth in this dorsal position would meet the opposition of the diaphragm, and the right ventricle would be forced ventrally. Since the left wall of the embryonic right ventricle is attached to the interventricular canal, ventral displacement can be accomplished only by a rotary anticlockwise motion, which when transmitted to the distal bulb would counteract the normal dextral torsion and result in transposition.

The expansion of the dorsal and lateral walls at the expense of the ventral wall might also result in the displacement ventrally of the supraventricular crest, the bulboatrial ledge, and the anterior tricuspid ledge, and in their intensification to form more or less complete septums across the ventricle. The ventral pouch bordered by such septums is not, however, the true right ventricle. Stenosis of the pulmonary artery may depend on the efficiency of such septums. Failure of the ventral sinusoids may cause the malformation or absence of the ventral interventricular septum, resulting in "crossed transposition."

"Overriding of the aorta" is due to arrest of development, as all mammalian embryonic hearts pass through this stage before the final separation of the ventricles by the growth of the membranous portion of the interventricular septum. This condition has no connection with transposition.

The main deductions of this paper rest chiefly on the tenuous basis of conditions found in a single human embryo, and are therefore submitted as a theory rather than as a proved exposition of the cause of the anomaly. Yet they trace the logical, mechanical effects of growth forces on an observed variation from normal, and show how these would result in transposition and its many accompanying changes in the heart.

AUTHOR.

Bayles, T. B.: Rheumatoid Arthritis and Rheumatic Heart Disease in Autopsied Cases. Am. J. M. Sc. **205:** 42, 1943.

Of twenty-three autopsied cases of rheumatoid arthritis, six were found to have changes in the heart valve leaflets and myocardium similar to those that usually follow rheumatic fever. The histologic lesions of one of these six could possibly be considered active and five were inactive in character. Excluding one patient because of definite rheumatic fever and rheumatic heart disease present in childhood, 22 per cent had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes ante mortem as compared to control groups, and the small number of cases (possibly one) with active rheumatic fever lesions have been pointed out. The rheumatoid arthritics in this apparently selected series have a rather high incidence of cardiac lesions similar to those that follow rheumatoid arthritis. A coincidence, a relationship of rheumatic fever and rheumatoid arthritis, or the possibility that the heart disease is related to rheumatoid arthritis, might be inferred from this data. Since patients with rheumatoid arthritis have to die of some other cause than their disease, it would be safer and probably wiser, as yet, to delay a final conclusion until further studies teach us which one of the above three situations truly obtains. In the clinical treatment of these patients, we have preferred to regard the cardiac changes as a coincidence of rheumatic heart disease and rheumatoid arthritis.

AUTHOR.

Bullrich, R. A.: Mitral Stenosis With Arterial Hypertension. Rev. argent. de cardiol. **9:** 87, 1942.

A review is made of observations reported in the literature of arterial hypertension coexisting with mitral stenosis, and thirteen cases of the same combination observed among one hundred and sixteen patients with mitral stenosis are reported and commented upon. It is the author's opinion that arterial hypertension observed in mitral stenosis has no relation to the valvular disease, and is a consequence of the survival of patients to an age where hypertension appears with equal frequency, and by the same causes, as in the general population. The increased percentage of women is due to the accidents of menopause. Arterial hypertension seems to have no influence on the evolution of cardiac insufficiency in patients with mitral stenosis.

AUTHOR.

Findley, T., Edwards, J. C., Clinton, E., and White, H. L.: Clearance of Diodrast, Phenolsulfonphthalein and Inulin in Hypertension and in Nephritis. Arch. Int. Med. **70:** 935, 1942.

Values for renal blood flow, glomerular filtration rate and tubular secretion of diodrast are reported on a series of normal subjects and patients with essential hypertension, glomerulonephritis and other types of renal disease.

Plasma clearances of diodrast and inulin, even when interpreted in the light of tubular secretion of diodrast, indicate absence of renal ischemia in a high proportion of subjects with uncomplicated essential hypertension.

Under controlled conditions the ratio between inulin clearance and diodrast clearance can represent the "filtration fraction," but high ratios in subjects with hypertension probably result from diminished diodrast extraction rather than from increased filtration pressure.

AUTHORS.

Dalton, J. W., and Nuzum, F. R.: Critical Statistical Analysis of Data on Renal Function in Grouped Subjects With Essential Hypertension. Arch. Int. Med. **70**: 948, 1942.

Instead of studying differences between single examples and noting variations between two random single samples, a more sensitive observation is made by comparing the results of renal function tests on patients with essential hypertension as a group, with results of the same tests on normal subjects as a group.

Working even in this manner we find that there is no variation of the renal function from the normal in a patient with essential hypertension because of the age of the patient, or because of the duration of the disease.

There is a retardation of the flow of urine in patients with hypertension having high diastolic pressures.

There is some indication of retardation of urinary flow and compensatory nocturia in hypertensive patients on an alkaline diet.

In general, there is fixation of specific gravity and retardation of phenolsulfonphthalein output in patients with hypertension.

The Volhard concentration and the phenolsulfonphthalein excretion test themselves are of no use clinically for the differential diagnostic purpose of distinguishing between persons with essential hypertension and normal persons in isolated instances. These studies indicate variation in the physiologic processes of the kidney due to a disease process coexistent with essential hypertension.

AUTHORS.

Dempsey, W. S.: The Adrenal Cortex in Essential Hypertension. Arch. Path. 34: 1031, 1942.

In a series of unselected routine autopsies on adult subjects, the adrenal glands were removed, fixed in dilute solution of formaldehyde, carefully dissected free of surrounding fat, and the adrenals from each subject weighed together. Paraffin sections were made from a block, cut transversely through the thickest part of each adrenal, and stained with hematoxylin and eosin.

Cases of essential hypertension and a group of nonhypertensive controls were segregated on the basis of rigid criteria. Other cases were appropriately grouped in separate categories.

The average weight of the adrenal glands in cases of essential hypertension is not significantly higher than that in nonhypertensive control cases.

Nodular or adenomatous hyperplasia of the adrenal cortex is not regularly found in association with essential hypertension, and it occurs with considerable frequency in nonhypertensive cases.

The microscopic appearance of tortuosity of the adrenal cortical cords and abundant deposition of fine lipoid droplets in the cortical cells is not consistently associated with the gross finding of irregularity and nodularity of the adrenal cortex.

AUTHOR.

Rich, A. R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa: Another Case Associated With a Sulfonamide Reaction. Bull. Johns Hopkins Hosp. **71**: 375, 1942.

In a previous paper the writer described a series of cases in which periarteritis nodosa was found at autopsy in patients who had had hypersensitive reactions resulting from foreign serum and sulfonamide therapy, and evidence was presented that periarteritis nodosa can be a manifestation of the anaphylactic type of hypersensitivity. The present report describes an additional case, in which periarteritis nodosa developed following a reaction (fever; conjunctivitis) to sulfathiazole.

This case is of particular interest for the reason that there was an opportunity to examine tissue removed from the patient's scrotum at five months and at one week before the sulfonamide reaction occurred, and nine days following the reaction. Periarteritis nodosa was not present in the specimens of scrotum removed before the reaction occurred. It was present there, and widespread throughout the body, following the reaction.

This case, in conjunction with the series described in the previous paper, is a further indication, derived from clinical and pathologic material, that periarteritis nodosa is a manifestation of anaphylactic type hypersensitivity.

In experiments carried out with Dr. John E. Gregory, to be reported presently, typical visceral periarteritis nodosa has been produced by the intravenous injection of a single, large amount of foreign serum into the normal animal, thus providing the opportunity for a protracted circulation of antigen while hypersensitivity develops.

These observations indicate that the continued administration of a sulfonamide or of foreign serum after symptoms of hypersensitivity have appeared, or the injection of a single large amount of foreign serum, carries the danger of producing vascular damage of the periarteritis nodosa type.

AUTHOR.

Sappington, S. W., and Fisher, H. R.: Arteriosclerosis Obliterans: A Study of the Lesions in Occluding Peripheral Sclerosis, With a Note on Mönckeberg's Sclerosis. Arch. Path. **34**: 989, 1942.

Forty-four cases of arteriosclerosis obliterans were studied by completely dissecting out the arterial trees from forty-four amputated gangrenous legs. This paper is a report of the vascular lesions present, together with deductions from the findings.

Gross study showed an extraordinary amount of arterial occlusion, averaging 44 per cent of the entire length of the anterior tibial, posterior tibial and peroneal arteries and indicating the great degree of arterial obstruction preceding gangrene.

Microscopic examination confirmed the gross estimate of arterial blockage. The average number of vessels occluded per case was 2.3. The occluding lesions apparently represented various stages and regressions of organizing obstructive clots. Atheroma was not a major or necessarily a participating feature. Vessels with the highest incidence of atheroma exhibited the lowest percentage of occlusions, while those with the highest incidence of closure presented the least degree of atheromatous involvement. It is suggested that abnormalities of the blood flow may be initiating factors in the formation of occluding clots.

The outstanding lesion of the media, calcification, was demonstrated in 100 per cent of thirty-eight cases roentgenologically and in 98 per cent of forty-four cases microscopically, but bone formation was also found in 70 per cent of the cases and a study of the obvious relationship between these two, leads us to conclude that, contrary to the usual conception, bone formation precedes calcification in the media in arteries of the legs, and probably accounts for the major part of the calcification found there.

AUTHORS.

Krupp, M. A.: Urinary Sediment in Visceral Angiitis (Periarteritis Nodosa, Lupus Erythematosus, Libman-Sacks "Disease"): Quantitative Studies. Arch. Int. Med. **71**: 54, 1943.

Twenty-one cases of periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks "disease" and the syndromes of Friedberg and Gross were studied with particular reference to the clinical manifestations of the renal lesion.

In seven cases no specific changes in urinary sediment were discovered, but in fourteen cases a singular picture of the sediment was observed. The uniqueness of this picture lies in the presence of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein in the same specimen of urine. These elements do not occur together in association with glomerulonephritis or with any other renal lesion with which the author is familiar.

This unusual sediment is of diagnostic value in doubtful cases of the disorders just mentioned.

The term visceral angiitis is advanced as a convenient clinical designation for these disorders and is not meant to imply a common etiologic relation.

AUTHOR.

Barman, J. M., Moreira, M. F., and Consolazio, F.: The Effective Stimulus for Increased Pulmonary Ventilation During Muscular Exertion. J. Clin. Investigation **22:** 53, 1943.

The increase in pulmonary ventilation has been studied in normal men exercising the limbs, first with normal circulation, and then with the circulation cut off by pressure from inflated cuffs.

Very light exercise (at a rate of 12 kilogrammeters per minute) of the flexors of the hand during total ischemia of the arms, usually resulted in a smaller ventilation than when the arms had normal circulation. Release of the ischemia was followed at once by a marked hyperventilation.

In subjects walking uphill on a treadmill (at a rate of 700 kilogrammeters per minute for a 90-kilo subject), total ischemia of both legs results in a marked diminution of pulmonary ventilation, even though the nervous pathways were intact, and release of the ischemia was followed at once by a marked hyperventilation, much higher than the value prior to ischemia.

These results are interpreted to mean that the chemical stimulus for increased ventilation in exercise of these types is far more important than the reflex.

The discrepancies between the authors' results and Harrison's are perhaps due to the fact that consistent results are found only after the subjects have become well accustomed to the experimental procedures by several repetitions of the experiments, and when exercise of sufficient severity is used so that the changes in ventilation and oxygen consumption are relatively large in magnitude.

AUTHORS.

Sigler, L. H.: Hyperactive Vasodepressor Carotid Sinus Reflex. Arch. Int. Med. **70:** 983, 1942.

This paper covers a study of the vasodepressor effect induced by the carotid sinus reflex. Seven hundred patients were tested, most of whom had demonstrable cardiovascular disease. Of these, 447 were males and 253 were females.

The patients were divided into four groups according to the original blood pressure. In Group I were included subjects with normal blood pressure; in Group II, patients with low grade hypertension; in Group III, those with moderate hypertension, and in Group IV those with marked hypertension.

It was found that, roughly, about 88 per cent of the males and 82 per cent of the females showed a drop in pressure. If a drop of less than 10 mm. is excluded as of insufficient significance, the response is reduced to about 78 per cent for males and 71 per cent for females. The response occurred more frequently and in greater degree in the older age groups. Also, the higher the blood pressure the more frequent the response and the greater its degree. A drop was more frequent in the systolic pressure than in the diastolic. A drop in pressure often occurred in patients with-

out cardioinhibition but was more frequent in those who also showed cardioinhibition. In such patients, the frequency and the degree of vasodepression roughly corresponded to those of cardioinhibition.

There was a marked difference in response to stimulation on the two sides in many cases. The amount of stimulation required to produce the maximum response varied from case to case and with the position of the patient.

The findings point to the existence of an inherent instability in the vasomotor system in persons who show a marked vasodepression induced by the carotid sinus reflex, which the test helps to demonstrate. The seat of this instability is either in the medullary synapses or in the vasomotor terminals in the vascular tree. Arteriosclerosis is possibly one of the underlying predisposing causes of such instability, as evidenced by the fact that the reflex is most prevalent under circumstances in which arteriosclerosis is apt to occur, that is, when the patient is a man, is of advanced age, and has a high degree of hypertension.

AUTHOR.

Starr, I., and Jonas, L.: Supernormal Circulation in Resting Subjects (Hyperkinemia) With a Study of the Relation of Kinemic Abnormalities to the Basal Metabolic Rate. Arch. Int. Med. **71**: 1, 1943.

In a total experience of about 1,400 estimations of cardiac output, one hundred patients were encountered in whom the resting circulation was above normal, a condition we have called hyperkinemia. These patients were usually underweight, and they tended to have resting pulse rates above normal.

Hyperkinemia was encountered in almost all patients with thyrotoxicosis without cardiac involvement and in most patients with patent ductus arteriosus. It was found often in patients with emaciation and less frequently in those with pulmonary abnormalities, fever, anemia, hypertension and peripheral arteriovenous communications.

In seventeen patients, hyperkinemia was present without any complicating condition having been discovered. These patients with essential hyperkinemia resembled patients with thyrotoxicosis in appearance, but the basal metabolic rate was always normal. The clinical characteristics of this subgroup have been described in detail.

The relation between abnormalities of the circulation and the basal metabolic rate has been studied by statistical methods. In uncomplicated hyperthyroidism and hypothyroidism the relation is almost 1 to 1; i.e., on the average, an abnormal increment or decrement in the basal metabolic rate is accompanied by an equal percentage change in the circulation. In heart disease these two functions are related, but the relationship is more nearly 1 to 0.5. Under such conditions the circulation is less than normal for any given metabolic rate, and the higher the metabolic rate the greater the circulatory deficit.

Other instances of deviation from the normal 1 to 1 relationship between circulation and metabolic rate have been found in cases of emaciation and in some cases of hyperthyroidism after partial thyroidectomy.

AUTHORS.

Leiter, L., Eichelberger, L., and Roma, M.: Studies on Renin: The Duration of the Pressor Effect of Large Doses in Conscious Normal and Renally Abnormal Dogs. Observations on Anesthetized and Uremic Dogs, and the Anaphylactic and Pathological Effects of Pig Renin. J. Clin. Investigation **22**: 11, 1943.

Trained, conscious dogs, injected with renin intravenously, in single moderate or large doses, sufficient to elevate the mean femoral blood pressure 50 to 100 mm. Hg, gave similar pressor responses whether their kidneys were normal or experimentally abnormal as the result of partial constriction of arteries or ureters, with or without nephrectomy.

Multiple doses of renin, or continuous injection by pump, produced a pressor plateau in renally normal and abnormal dogs, but the blood pressure returned to the control level within an hour after the injection in all of the normal animals and in most of the dogs with unilateral or less extensive bilateral renal lesions.

Marked prolongation of renin pressor activity was observed chiefly in dogs with bilateral, experimental, renal abnormalities following multiple doses or continuous injection of kidney extract, free from depressor material.

Prolonged duration of renin pressor activity also occurred in anesthetized, renally normal dogs and in the majority of conscious dogs with uncomplicated uremia. Dogs with experimental hypertension and uremia reacted irregularly.

Repeated experiments on the same animal with heterologous renin led to the development of anaphylaxis. Dogs sensitized to pig renin reacted normally to dog renin.

The pathologic lesions of experimental malignant hypertension can be induced or accelerated by the injection of foreign renin, not only in dogs with excessive renal ischemia or necrosis, but in some animals without severe hypertension or uremia.

The prolonged effect of renin in conscious dogs with extensive renal abnormality is regarded as evidence in favor of the renin etiology of experimental renal hypertension, and in support of the view that the ratio of normal to abnormal (''ischemic'') renal parenchyma is a determining factor in the dog's response to exogenous, as well as endogenous, renin.

The relation of renin to human ''essential'' hypertension remains an open question.

AUTHORS.

Book Reviews

VASCULAR SPASM. EXPERIMENTAL STUDIES: By A. J. Nedzel, M.D., Associate Professor of Pathology, University of Illinois. University of Illinois Press, 1943, 151 pages, 161 illustrations, $2.75.

This monograph is devoted chiefly to the presentation of the thesis that vascular spasm is the initial step in the production of the lesions of such diverse diseases as endocarditis, gastric ulcer; and multiple sclerosis. The evidence marshalled in support of the author's position was obtained from experiments on dogs in which, as the author admits, "highly exaggerated" vascular spasm was produced by repeated injections of large doses of pitressin. One wonders whether an equally good case could be made for injections of preparations that act on the vascular bed in a direction opposite to pitressin. It is now well established that animals which are required to absorb appropriate doses of histamine for weeks develop gastric ulcer in a high percentage of cases.

The author's thesis might have been strengthened by positive evidence from experiments in which epinephrine or some other sympathicomimetic drug was used in more nearly physiologic doses.

The monograph should prove of much value to those who are interested in the pathologic effects of large doses of pitressin, which the author has presented in considerable detail. Many will be especially interested in the summaries of the literature in the various sections of the book. The work is excellently printed and is effectively illustrated.

HIRAM E. ESSEX.

A SHORT HISTORY OF CARDIOLOGY: By James B. Herrick, M.D., Emeritus Professor of Medicine, Rush Medical College, Chicago, Ill. Charles C Thomas, Springfield, Ill., 1942, 258 pages, 49 illustrations, $3.50.

It has often been said that no one should be allowed to enter medical school until he has read Vallery-Radot's *Life of Pasteur,* or the experimental laboratory until he has read Claude Bernard's *Introduction to the Study of Experimental Medicine.* Likewise, Dr. Herrick's monograph is a prerequisite for anyone who aspires to be a cardiologist. It is more comprehensive than R. O. Moon's *Growth of Our Knowledge of Heart Disease* and Rolleston's delightful Harveian Oration on *Cardio-Vascular Diseases Since Harvey's Discovery.* One is struck by the author's dispassionate treatment of controversial questions and his judicious appraisal of men and their work. Much of the material is not new, of course, but the approach often is, and some neglected aspects of the subject have been given the attention which they deserve. Throughout the book one notes the healthy skepticism about "priority" which is so important for sound historiography. The fact that there is no substitute for experience is reflected on almost every page. One who had not lived a long and observant life and had not himself been intimately in contact with many stirring events of medical history could scarcely have written this book.

HORACE M. KORNS.

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